ACP | MKSAP® 19

Medical Knowledge Self-Assessment Program®

Gastroenterology and Hepatology

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Leading Internal Medicine, Improving Lives

Welcome to the Gastroenterology and Hepatology Section of MKSAP 19!

In these pages, you will find updated information on gastroesophageal reflux disease, Barrett esophagus, *Helicobacter pylori* infection, gastrointestinal bleeding, gastrointestinal complications of NSAIDs, celiac disease, inflammatory bowel disease, liver disease, gallbladder disease, and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of gastroenterology and hepatology.

MKSAP 19 strives to provide the clinical knowledge its learners need to navigate their longitudinal learning paths. MKSAP 19's core content contains essential, newly researched information in 11 subspecialty areas of internal medicine–created by dozens of expert generalists and subspecialists. Development of MKSAP 19's syllabus and its 1200 all-new, peer-reviewed, psychometrically validated multiple-choice questions (MCQs) has been informed by ABIM Certification and Maintenance of Certification (MOC) requirements, emerging internal medicine knowledge, and our learners' feedback. MKSAP 19 continues to include *High Value Care* (HVC) recommendations and MCQs, based on the concept of balancing clinical benefit with costs and harms. Hospital-based internists can continue to trust that MKSAP's comprehensive hospitalist content, integrated throughout the syllabus, and hospitalist-focused MCQs, specially designated with the blue hospitalist icon (H), continue to align with the ABIM's Focused Practice in Hospital Medicine MOC exam blueprint and enhance learning for hospital-based practitioners.

More than ever before, MKSAP 19 Digital focuses on individualized learning and convenience. In addition to custom quizzes and interlinked questions and syllabus sections, MKSAP 19 Digital's new learning dashboard enables users to create a self-directed learning plan, with topic-specific links to resources within MKSAP and ACP Online. Multimedia formats, including whiteboard animations and clinical videos, will benefit our audiovisual learners, while MKSAP's Earn-as-You-Go CME/MOC feature now allows subscribers to earn CME/MOC as they answer individual questions. In addition to Extension Questions and New Info Updates, MKSAP 19 Complete and Complete Green continue to offer Virtual Dx and Flashcards and now offer brand-new enhancements: MKSAP Quick Qs, a set of concise questions mapped to high-frequency/high-importance areas of the ABIM blueprint mirroring boards-style MCQs, and an embedded digital version of Board Basics for easy-access exam prep.

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On behalf of the many internists and editorial staff who have helped us create our new edition, we are honored that you have chosen to use MKSAP 19 to meet your lifelong learning needs.

Sincerely,

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MKSAP Resource Page

The MKSAP Resource Page (www.acponline.org/mksap19-resources) provides access to MKSAP 19 online answer sheets for transcribing answers from the print edition; access to MKSAP 19 Digital; Board Basics®; information on Continuing Medical Education (CME), Maintenance of Certification (MOC), and international Continuing Professional Development (CPD) and MOC; errata; and other new information.

International MOC/CPD

Information and instructions on submission of international MOC/CPD is available by accessing the CME/MOC/CPD tab on the left navigation menu of MKSAP 19 Digital.

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The American College of Physicians is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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Up to 24 *AMA PRA Category 1 Credits*™ are available from August 31, 2021, to August 31, 2024, for the MKSAP 19 Gastroenterology and Hepatology section.

Learning Objectives

The learning objectives of MKSAP 19 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve clinical management decisions that affect patient safety and quality of care
- Determine when to refer patients for care by medical subspecialists, surgeons, and other members of the health care team
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internal medicine specialists, including primary care physicians and hospitalists
- Internal medicine subspecialists who desire to remain up to date in internal medicine
- Residents preparing for the ABIM Internal Medicine Certification Examination
- Physicians engaged in the ABIM Maintenance of Certification Longitudinal Assessment Option, preparing for the ABIM Internal Medicine Maintenance of Certification Examination, or engaged with the ABIM Focused Practice in Hospital Medicine program

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To earn CME credits or to apply for MOC points, MKSAP users need to answer at least one of two questions correctly (earning a score of at least 50%) and click the Submit CME button. Each single MKSAP 19 self-assessment question qualifies for one quarter of a CME credit hour or ABIM MOC point.

MKSAP 19 Subscribers can enter their self-assessment question answers and submit for CME/MOC in two ways:

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Hospital-Based Medicine

For the convenience of subscribers who provide care in hospital settings, comprehensive hospital-focused content aligned with the ABIM Focused Practice in Hospital Medicine blueprint is integrated throughout the syllabus, and self-assessment questions that are specific to the hospital setting are specially designated with the blue hospitalist icon (H).

High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [HVC].

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Errata and Revisions

Errata and Revisions for MKSAP 19 will be available through MKSAP 19 Digital at mksap19.acponline.org as new information becomes known to the editors.

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Gastroenterology and Hepatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 19 in several important ways. MKSAP 19 includes HVC-identified key points in the text, HVC-focused multiple-choice questions, and, in MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Gastroenterology and Hepatology section of MKSAP 19.

- In patients with symptoms of gastroesophageal reflux disease but without alarm features, an empiric trial of a proton pump inhibitor is the initial management.
- *Candida* esophagitis can be diagnosed clinically in patients with dysphagia and odynophagia, immunosuppression, and findings of oral thrush (see Item 89).
- PPI therapy should be used at the lowest dose needed to control gastroesophageal reflux symptoms and discontinued if there is no appropriate indication (see Item 44).
- For patients with dyspepsia, routine upper endoscopy to exclude malignancy is reserved for patients age 60 years and older.
- In countries with a low incidence of gastric cancer, such as the United States, screening for gastric cancer should be reserved for patients with genetic cancer syndromes.
- For patients with dyspepsia, a “test and treat” strategy for *Helicobacter pylori* infection is recommended (see Item 70).
- Routine repeat upper endoscopy for gastric ulcer is not recommended (see Item 73).
- Patients with acute pancreatitis should undergo transabdominal ultrasonography rather than CT for evaluation of biliary disease.
- Routine use of antibiotics is not warranted in acute pancreatitis (see Item 12).
- Patients with acute pancreatitis should resume feeding when pain improves and any nausea or vomiting subsides; oral feeding is preferred (see Item 16).
- Evaluation for centrally mediated pain syndrome requires a detailed medical and psychosocial history and physical examination, with limited laboratory testing.
- Acute diverticulitis is often a clinical diagnosis, usually not requiring abdominal imaging unless an alternative diagnosis or complicated disease is suspected.
- Lactase deficiency can be diagnosed on the basis of improvement after exclusion of dietary lactose or administration of lactase enzymes with meals (see Item 37).
- The most common cause of recurrent celiac disease symptoms is gluten exposure (see Item 45).
- Many drugs can cause chronic diarrhea; discontinuing a potential culprit drug may relieve symptoms and obviate the need for further diagnostic testing (see Item 59).
- Antibiotics are not recommended for mild traveler’s diarrhea (see Item 86).
- Irritable bowel syndrome is a common cause of diarrhea and can be diagnosed on clinical grounds, including history and physical examination (see Item 22).
- Empiric antibiotic therapy with monitoring for improvement in symptoms may be reasonable in patients with a high probability of small intestinal bacterial overgrowth (see Item 67).
- Elastography is a noninvasive imaging technique that assesses liver stiffness as a measure of fibrosis and may avoid biopsy.
- Asymptomatic hepatic cysts are benign and require no follow-up.
- Focal nodular hyperplasia does not have malignant potential or a risk for bleeding and does not require follow-up.
- No information indicates that the addition of α-fetoprotein (AFP) to ultrasonography screening for hepatocellular carcinoma leads to improved survival; therefore, surveillance using ultrasonography may be performed with or without AFP measurement every 6 months (see Item 30).
- The mainstay of management of nonalcoholic fatty liver disease is weight loss (see Item 35).
- Management of chronic pain in patients with chronic liver disease should always include physical therapy

because it will not exacerbate the manifestations of chronic liver disease (see Item 82).

- Patients in the immune control phase of chronic HBV infection, also known as inactive chronic HBV infection, generally do not require treatment (see Item 4).
- Uncomplicated diverticulitis is treated with oral antibiotics (ciprofloxacin or metronidazole) and a liquid diet (see Item 6).
- Incidental gallstones do not typically cause symptoms, and prophylactic cholecystectomy and other treatments are generally not recommended (see Item 78).
- In acute cholecystitis, cholecystectomy during the initial hospitalization is associated with improved clinical outcomes and lower costs compared with delayed cholecystectomy (see Item 74).
- For patients with mild gallstone pancreatitis, same-admission cholecystectomy reduces rates of gallstone-related complications compared with cholecystectomy 25 to 30 days after hospital discharge (see Item 96).
- Patients with peptic ulcer disease and low-risk stigmata can be fed within 24 hours of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital.
- In uncomplicated asymptomatic patients with iron deficiency anemia and negative bidirectional endoscopy, a trial of initial iron supplementation over the routine use of video capsule endoscopy is conditionally suggested by the American Gastroenterological Association (see Item 60).
- The risk for rebleeding in patients with high-risk ulcers that are successfully treated endoscopically is similar for patients who receive twice-daily intravenous PPI and those who receive continuous PPI infusion; twice-daily PPI is preferable given the similar clinical efficacy and lower cost (see Item 88).
- When there is no evidence that a patient's requested diagnostic or therapeutic intervention will provide clinical benefit, physicians are not obligated to provide the service (see Item 58).

Gastroenterology and Hepatology

Disorders of the Esophagus

Symptoms of Esophageal Disease

Dysphagia

Normal swallowing consists of three phases. The oral phase encompasses formation of a food bolus and transfer of the bolus to the back of the throat. The pharyngeal phase allows the bolus to be safely positioned in the upper throat; the soft palate elevates, the epiglottis protects the trachea, the tongue moves backward, and the pharyngeal wall moves forward. The esophageal phase starts with the bolus entering the esophagus with relaxation of the upper esophageal sphincter. Peristalsis (rhythmic contractions) propels the bolus down; primary peristalsis is initiated with the swallow, and secondary peristalsis is intended to clear residual bolus. This phase ends as the lower esophageal sphincter relaxes to allow the bolus to enter the stomach.

Dysphagia is a disruption in the swallowing mechanism, resulting in a bolus not passing from the mouth to the stomach. Determining whether the cause is oropharyngeal or esophageal is important in developing a differential diagnosis and management plan. **Table 1** highlights common causes of dysphagia.

Oropharyngeal Dysphagia

Oropharyngeal dysphagia, also called transfer dysphagia, occurs when the patient cannot transfer the food bolus from the mouth into the upper esophagus by swallowing. Common symptoms include choking, coughing, and nasal regurgitation of food and liquids. Patients are at risk for aspiration pneumonia. Stroke is a common cause, and an underlying neurologic disorder, such as Parkinson disease, may be suspected, particularly with concurrent neurologic findings. A pharyngoesophageal (Zenker) diverticulum should be considered when undigested food is brought up several hours after a meal or if a patient reports hearing a gurgling noise in the throat.

The initial study for suspected oropharyngeal dysphagia is a modified barium swallow and video fluoroscopy, with a range of liquid and solid consistencies. Routine upper gastrointestinal endoscopy and esophageal manometry have a limited role in the evaluation of oropharyngeal dysphagia. Management includes dietary changes and a swallowing exercise program implemented with a speech pathologist.

Esophageal Dysphagia

Patients with esophageal dysphagia can initiate the swallowing process but often feel chest discomfort. Patients also may not readily characterize dysphagia as difficulty swallowing. Common descriptions of the sensations of dysphagia include food "hanging up" or feeling lodged or stuck during a meal. Patients also may describe a bolus slow to go down or "sitting" in the chest. Occasionally they may present with vomiting of undigested food contents.

Esophageal dysphagia results from one of two causes: a mechanical obstruction or a motility disorder. Dysphagia with solids alone suggests a mechanical obstruction, whereas dysphagia with liquids alone or with liquids and solids favors a motility disorder. An urgent workup is indicated for complete obstruction, hematemesis, odynophagia, onset in an older patient, dysphagia associated with weight loss, or acute course. Food impaction may occur, wherein a food bolus lodges in the esophagus and obstructs the passage of additional food, fluid, or saliva. Food impaction is an indication for emergency endoscopy.

Mechanical esophageal obstruction may be benign or malignant and may be caused by masses, strictures, an esophageal ring (e.g., a Schatzki ring [**Figure 1**]), webs, or complex hiatal hernias. Strictures may be due to chronic reflux esophagitis (peptic strictures), eosinophilic esophagitis, radiation therapy, or caustic injury. Dysphagia that progresses from occurring only with solids to occurring with both solids and liquids is concerning because it may be indicative of malignancy or of benign strictures that have become high-grade obstructions. Achalasia often presents with dysphagia for both solids and liquids associated with nonacidic regurgitation of undigested food and fluid. Chest pain upon ingestion of very hot or very cold liquids may indicate esophageal spasm.

Upper endoscopy allows for diagnosis (biopsy and inspection) and therapeutic intervention (dilation) and is the usual initial test of choice. Barium esophagography may provide more information in specific situations, such as suspicion of motility disorders or proximal lesions (e.g., Zenker diverticulum). Clinical management is based on the underlying cause.

Odynophagia

Pain while swallowing defines odynophagia and suggests active mucosal inflammation and esophageal ulceration. Odynophagia is commonly associated with pill-induced damage, infection, or caustic ingestion and is less commonly caused by gastroesophageal reflux disease (GERD) or esophageal cancer. Upper endoscopy with biopsy is the most

TABLE 1. Causes of Dysphagia

Condition	Diagnostic Clues
Oropharyngeal Dysphagia	
Structural disorders	
Cervical osteophytes	High dysphagia, degenerative joint disease
Cricoid webs	High dysphagia, iron deficiency
Pharyngoesophageal (Zenker) diverticulum	Aspiration, neck mass, and regurgitation of foul-smelling food
Goiter	Neck mass
Neurologic/myogenic disorders	
Amyotrophic lateral sclerosis	Upper and lower motoneuron signs, fasciculations
Central nervous system tumor	Headache, vision changes, nausea, seizures, balance problem
Stroke	Focal neurologic deficits
Muscular dystrophy	Slow progression of muscular weakness over years
Myasthenia gravis	Weakness with repetitive activity
Multiple sclerosis	Episodes of neurologic dysfunction with variable degrees of recovery
Parkinson disease	Bradykinesia, rigidity, tremor
Dementia	Altered cognition
Sjögren syndrome	Dry mouth, dry eyes
Esophageal Dysphagia	
Structural disorders	
Dysphagia lusoria (vascular dysphagia)	Vascular extrinsic compression of the esophagus on imaging
Epiphrenic/traction diverticulum	Outpouching of the esophagus at any level on imaging
Esophageal strictures	Progressive dysphagia, especially for solid food; history of reflux
Eosinophilic esophagitis	Food impactions, atopic history, rings or strictures on endoscopy
Esophageal webs or rings	Intermittent dysphagia; upper esophageal webs may be associated with iron deficiency anemia
Neoplasms	Rapidly progressive dysphagia for solids, then liquids; anorexia; weight loss
Motility disorders	
Achalasia	Concomitant liquid and solid dysphagia
Diffuse esophageal spasm	Chest pain
Systemic sclerosis	Skin hardening, telangiectasias, sclerodactyly, gastroesophageal reflux disease, Raynaud phenomenon

appropriate diagnostic test to determine the degree of inflammation and underlying cause.

Globus Sensation

Patients commonly report globus sensation as a lump in the throat or throat tightness, usually not linked to meals. Causes of globus include GERD (with or without heartburn), motility disorders, stress, and psychiatric conditions (e.g., anxiety disorder, panic disorder, and somatic symptom disorder). Globus should not be diagnosed if the patient reports other esophageal symptoms, such as dysphagia or odynophagia. Assessment for the cause should include evaluation for thyroid goiter and an underlying pharyngeal lesion, which can be diagnosed by transnasal endoscopy or barium swallow.

Treatment with acid suppression or cognitive behavioral therapy may be initiated once a structural cause has been ruled out.

Reflux and Chest Pain

The development of chest pain from an esophageal cause can mimic chest pain from cardiac disease. A cardiac cause must be ruled out first. The most common cause of noncardiac chest pain is GERD. Another possible cause is an esophageal motility disorder, particularly hypercontractile motility disorders. Reports of heartburn with a history of Raynaud phenomenon could signify a systemic condition, such as systemic sclerosis. Starting a course of an acid-reducing agent can be both diagnostic and therapeutic. Patients whose symptoms do not respond require further evaluation, including upper

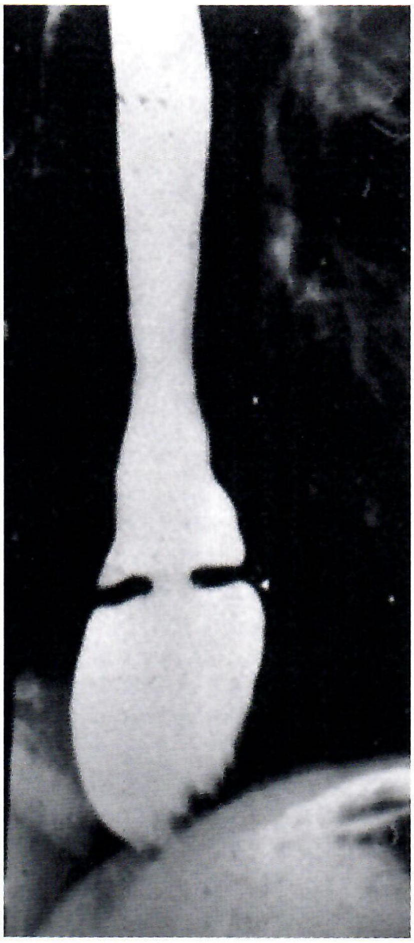

FIGURE 1. Barium esophagram showing a Schatzki ring, a subtype of esophageal ring located at the squamocolumnar junction and a common cause of dysphagia.

endoscopy, and possibly ambulatory pH testing with or without esophageal manometry.

See Gastroesophageal Reflux Disease for information about diagnosis and management.

KEY POINTS

- Oropharyngeal dysphagia occurs when the patient cannot transfer the food bolus from the mouth into the upper esophagus by swallowing and should be evaluated with a modified barium swallow with video fluoroscopy.
- Esophageal dysphagia with solids alone suggests a mechanical obstruction, whereas dysphagia with liquids alone or with liquids and solids favors a motility disorder.
- Upper endoscopy is diagnostic and may be therapeutic for esophageal dysphagia.
- Chest pain is common in patients with gastroesophageal reflux disease, but a cardiac cause of chest pain must be ruled out first.

TABLE 2. Factors Associated With Reflux

Category	Factor
Lifestyle	Cigarette smoking
Eating habits	Eating large meals
	Eating late at night
	Lying supine shortly after eating
Foods and beverages	Alcohol
	Chocolate
	Citrus fruits and juices
	Coffee
	Fatty and fried foods
	Onions
	Peppermint
Medications	Anticholinergic agents
	Aspirin and NSAIDs
	Calcium channel blockers
	Nitrates
	Progesterone
	Opioids (due to delayed gastric emptying)
Body position	Bending over, exercising (both result in increased intra-abdominal pressure)
Other	Obesity
	Pregnancy
	Tight-fitting clothing
	Hiatal hernia

Nonmalignant Disorders of the Esophagus

Gastroesophageal Reflux Disease

GERD is characterized by contents refluxing from the stomach into the esophagus. It has a prevalence of 10% to 20% in the Western world. There is a strong relationship between GERD and obesity. The most common symptoms reported are heartburn, regurgitation, and chest pain, for which a cardiac cause must be excluded. Many factors can trigger reflux (**Table 2**). Protective mechanisms to minimize esophageal exposure to acid and its effects include swallowed salivary bicarbonate, peristalsis, a competent lower esophageal sphincter (LES), and gastric emptying; reflux occurs when these physiologic protectors become ineffective. Uncontrolled GERD can negatively affect quality of life because of poor sleep, low productivity, and work absences. Long-standing GERD can lead to complications, including reflux esophagitis, stricture, Barrett esophagus, and esophageal adenocarcinoma. Commonly attributed extraesophageal conditions include chronic cough, hoarseness (laryngitis), wheezing (asthma), and dental erosions. Pregnant women may experience GERD during any trimester of pregnancy, symptoms may worsen as the pregnancy progresses, and symptoms typically resolve after delivery.

Diagnosis

Strategies for diagnosing GERD include consideration of clinical history and response to medical therapy; testing, such as endoscopy and ambulatory pH monitoring; and exclusion of a motility disorder by manometry. There is no single gold-standard diagnostic test. Clinical symptoms of heartburn and regurgitation strongly suggest GERD. Alarm features include dysphagia, weight loss, hematemesis, or melena. Patients with GERD symptoms but without alarm features may undergo an empiric trial of a proton pump inhibitor (PPI). In patients with alarm features or failure to respond to treatment, upper endoscopy is warranted to rule out an underlying ring, web, malignancy, eosinophilic esophagitis, erosive esophagitis, stricture, or Barrett esophagus. Most patients with GERD have normal findings on upper endoscopy.

Ambulatory pH monitoring can quantify acid exposure in the esophagus. Impedance-pH testing can help differentiate between acid and nonacid reflux. Testing to detect active acid reflux can be done with a 24-hour transnasal catheter or 48-hour or 96-hour wireless capsule endoscopy. pH monitoring may be performed while the patient is not receiving acid-suppressive therapy to confirm acid exposure and support a diagnosis of GERD. Esophageal manometry should be considered as part of the evaluation for patients with dysphagia or atypical reflux symptoms and before antireflux surgery to rule out motility disorders.

Treatment

An algorithm outlining evaluation of GERD is presented in **Figure 2**.

Lifestyle Changes

Patients with recent weight gain or who are overweight should have a weight-loss plan. Patients with nocturnal GERD should not eat within at least 3 hours before going to sleep and should consider raising the head of the bed. Avoiding large meals and rich or fatty foods that stay in the stomach for longer periods is helpful.

Additional dietary modification should focus on eliminating specific foods that trigger an individual patient's GERD symptoms rather than globally eliminating all common trigger foods (caffeine; chocolate; spicy foods; acidic foods, such as citrus fruits; and fatty foods). Cessation of alcohol and tobacco use is recommended.

Medical Therapy

Pharmacologic therapy includes antacids, H_2 blockers, and PPIs. A PPI once daily for 8 weeks is the therapy of choice for symptom relief and for treatment of erosive esophagitis. Most PPIs should be taken once daily, 30 to 60 minutes before the first meal of the day. Patients with partial response to PPI therapy should increase the dosage to twice daily. Given the risks and potential adverse effects of PPI therapy (**Table 3**), the goal should be to use the lowest dose required to control symptoms and to discontinue if there is not an appropriate indication. Similarly, patients requiring long-term maintenance therapy should be prescribed the lowest effective PPI dose, including on-demand or intermittent use. For patients with uncomplicated GERD, stopping or reducing long-term PPI therapy should be attempted once a year.

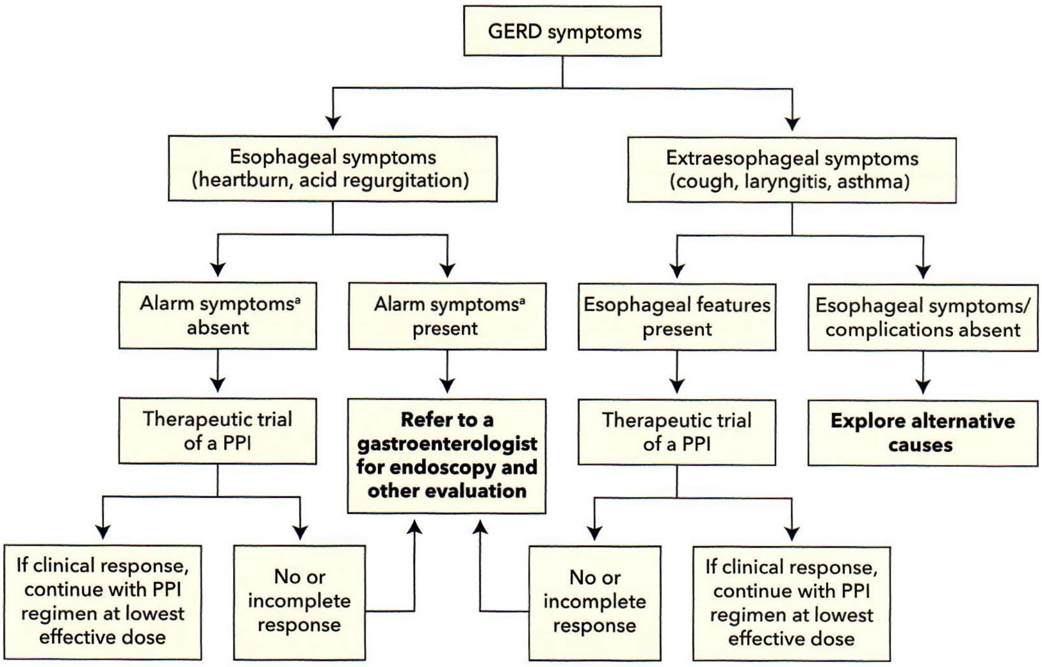
GERD symptoms
Esophageal symptoms (heartburn, acid regurgitation)
Extraesophageal symptoms (cough, laryngitis, asthma)
Alarm symptoms[a] absent
Alarm symptoms[a] present
Esophageal features present
Esophageal symptoms/ complications absent
Therapeutic trial of a PPI
Refer to a gastroenterologist for endoscopy and other evaluation
Therapeutic trial of a PPI
Explore alternative causes
If clinical response, continue with PPI regimen at lowest effective dose
No or incomplete response
No or incomplete response
If clinical response, continue with PPI regimen at lowest effective dose

FIGURE 2. Management of gastroesophageal reflux disease.

GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.

[a]Alarm symptoms include dysphagia, unintentional weight loss, hematemesis, and melena.

TABLE 3. Adverse Effects of Proton Pump Inhibitors

Common	Unusual	Proposed Associations
Headache	Vitamin B_{12} deficiency	Kidney injury[a]
Diarrhea	Hypomagnesemia	Dementia[a]
Dyspepsia	Community-acquired pneumonia[a]	
	Clostridioides difficile infection[a]	
	Hip fracture	

[a]A large randomized controlled trial published in 2019 failed to demonstrate increased risk for these outcomes over 3 years (Moayyedi P, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology. 2019;157:682-691.e2. [PMID: 31152740] doi:10.1053/j.gastro.2019.05.056).

Switching to a different PPI may be warranted for adverse reactions or unresponsive symptoms. PPIs are safe in pregnant patients.

Prokinetic agents, such as metoclopramide, should not be used to treat GERD unless gastroparesis is present.

Antireflux Surgery

Surgery is infrequently required; indications include failure of optimal PPI therapy, a desire to stop the medication, and intolerable medication side effects. Patients should undergo objective testing, such as pH monitoring and manometry, before surgery. Surgical treatments for GERD are laparoscopic fundoplication or bariatric surgery for obesity as well as magnetic sphincter augmentation (a magnetic ring is placed around the LES without surgical alteration of the stomach). Surgery is most effective in patients with typical symptoms of heartburn and regurgitation that respond to PPI therapy. However, about one third of patients require resumption of a PPI 5 to 10 years after surgery. Postoperative complications include dysphagia, diarrhea, and inability to belch because of a tight fundoplication.

Endoscopic Therapy

Transoral incisionless fundoplication (an endoscopic fundoplication created with full-thickness suture) has had initial success; long-term data are limited. Additional endoscopic therapies for GERD are based on thermal radiofrequency energy, silicone injection, suturing, and endoscopic resection, but long-term benefits are unproven.

Extraesophageal Manifestations

Asthma, chronic cough, and laryngitis are linked to GERD (see Figure 2). When these symptoms are present, other non-GERD causes should be eliminated. Laryngoscopy should not be used to diagnose GERD-related laryngitis, and edema and erythema as potential signs of reflux-induced laryngitis are nonspecific. A PPI trial is recommended in patients who have concomitant typical GERD symptoms. For patients with atypical symptoms only, ambulatory esophageal pH monitoring should be considered before a PPI trial. Surgery is less effective in this group and should be considered only in patients whose symptoms respond to PPI therapy.

Refractory GERD

The first step in addressing refractory GERD is to optimize PPI therapy by emphasizing the importance of taking medication 30 to 60 minutes before eating, increasing the dosage to twice daily, or switching to another PPI. If symptoms are still unresponsive, alternative causes must be considered. For typical symptoms, endoscopy is used to rule out eosinophilic esophagitis or erosive esophagitis. Adequacy of acid suppression therapy may be confirmed by esophageal impedance-pH testing while the patient is receiving optimized PPI therapy. For atypical symptoms, other causes should be evaluated, and referral to otorhinolaryngology, pulmonary, or allergy specialists to identify and treat the cause should be considered. In these patients, impedance-pH testing conducted off acid-suppression therapy may help confirm the diagnosis of acid reflux. If results of impedance-pH and pH testing are normal but symptoms persist, therapy for functional heartburn may be attempted with selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is commonly associated with dysphagia and food bolus obstruction, which may be recurrent. Most patients are diagnosed between the second and fifth decades of life, and EoE is more common in men. Patients often have other atopic conditions, such as asthma, rhinitis, dermatitis, and seasonal or food allergies. The reported U.S. prevalence is 40 to 90 per 100,000. The diagnostic criteria for EoE are esophageal symptoms (dysphagia), esophageal biopsy specimens showing persistent eosinophil counts of 15/hpf or greater, and exclusion of other causes of eosinophilia. Other causes include GERD, hypereosinophilic syndrome, infections (fungal, viral), autoimmune and connective tissue disorders, Crohn disease with esophageal involvement, and drug hypersensitivity reactions. EoE is diagnosed in the absence of eosinophilia elsewhere.

Endoscopic findings include rings, longitudinal furrows, luminal narrowing, and sometimes strictures (**Figure 3**). If assessment identifies no other causes of eosinophilia, EoE can be diagnosed and appropriate therapy initiated with a PPI and/or swallowed topical glucocorticoids (fluticasone or budesonide). Limited evidence suggests that diet modification may be effective in the prevention of EoE. An empiric elimination diet–removing the foods most commonly associated with food allergies, such as egg, soy, wheat, peanuts, cow's milk, and fish/shellfish–has been used. Endoscopic dilation should be considered in patients with continued dysphagia caused by esophageal stricture not responding to medical therapy.

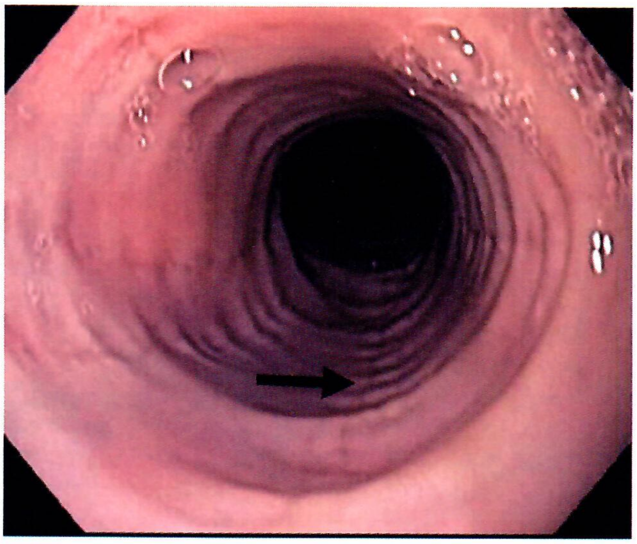

FIGURE 3. The characteristic findings of eosinophilic esophagitis on endoscopy include rings and longitudinal furrows; strictures may also be seen.

Infectious Esophagitis

Infectious esophagitis can be caused by fungal, viral, bacterial (uncommon), or parasitic pathogens. It most commonly occurs in immunocompromised patients. Patients most often present with odynophagia or dysphagia. *Candida* esophagitis frequently causes dysphagia with or without odynophagia, whereas viral esophagitis produces odynophagia. Other organisms associated with esophagitis include *Lactobacillus*, β-hemolytic streptococci, *Cryptosporidium* species, *Pneumocystis jirovecii*, *Mycobacterium avium* complex, and *Mycobacterium tuberculosis*.

Candida infection can occur in immunocompetent or immunocompromised hosts. Diagnosis is usually made clinically on the basis of compatible symptoms and oral candidiasis, although not all patients have oral involvement. Endoscopy and biopsy can be considered for patients who do not respond to empiric therapy or who have atypical symptoms. Endoscopy shows small, white, raised plaques, and esophageal brushings confirm the diagnosis (**Figure 4**). The most common species is *Candida albicans*, which is treated with oral fluconazole.

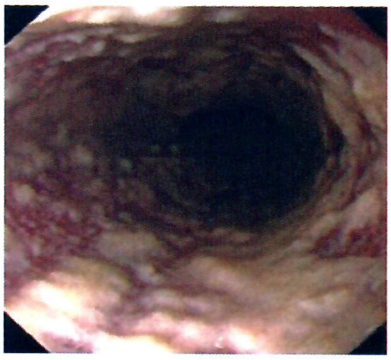

FIGURE 4. White adherent plaques suggesting *Candida* esophagitis, as seen on upper endoscopy.

Herpes simplex virus and cytomegalovirus are seen in immunodeficient or immunosuppressed individuals but rarely occur in immunocompetent patients. Endoscopy with biopsy is needed to confirm the diagnosis. Herpes simplex virus infection is treated with acyclovir, and cytomegalovirus infection is treated with ganciclovir; oral valganciclovir is also an option.

Pill-Induced Esophagitis

Medications can cause esophageal injury that results in esophagitis. Risk factors for pill-induced esophagitis include decreased salivary output, esophageal dysmotility, large pills, medications that increase the LES tone (opioids), and ingestion of medications in the supine position. Patients commonly report chest pain, dysphagia, and odynophagia several hours to days after taking the medication. Pill-induced esophagitis has occurred with alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine. Medications associated with stricture formation include alendronate, ferrous sulfate, NSAIDs, and potassium chloride. Pill-induced esophagitis can be diagnosed by history alone, but upper endoscopy should be performed for severe symptoms, persistent symptoms, or atypical symptoms (such as hematemesis or abdominal pain). Preventive strategies include drinking sufficient water with medications and remaining upright for 30 minutes after pill ingestion.

Esophageal Motility Disorders

The esophagus is a muscular tube that passes a food bolus from the hypopharynx to the stomach through peristalsis. The upper third of the esophagus is composed of skeletal muscle innervated by axons of lower motor neurons. The lower two thirds is smooth muscle innervated by the vagus nerve. High-resolution esophageal manometry is used to evaluate suspected esophageal motility disorders.

Hypertonic Motility Disorders

Hypertonic motility disorders are characterized by dysphagia with both liquids and solids. Other symptoms can include regurgitation of undigested food, particularly when the patient is in a recumbent position.

Achalasia and Pseudoachalasia

Achalasia is defined by inadequate relaxation of the LES and aperistalsis. Achalasia can be idiopathic or associated with viral, autoimmune, and neurodegenerative disorders and infection (Chagas disease). Damage to the ganglion cells and myenteric plexus in the esophageal body and LES leads to uncontested cholinergic nerve activation, which prevents LES relaxation. Achalasia affects men and women equally, with an annual incidence of 1 in 100,000 individuals. It commonly occurs between 30 and 60 years of age. Patients have dysphagia with both solids and liquids along with nonacidic regurgitation of undigested food. Additional symptoms include heartburn, weight loss, and chest pain unresponsive to acid-reducing

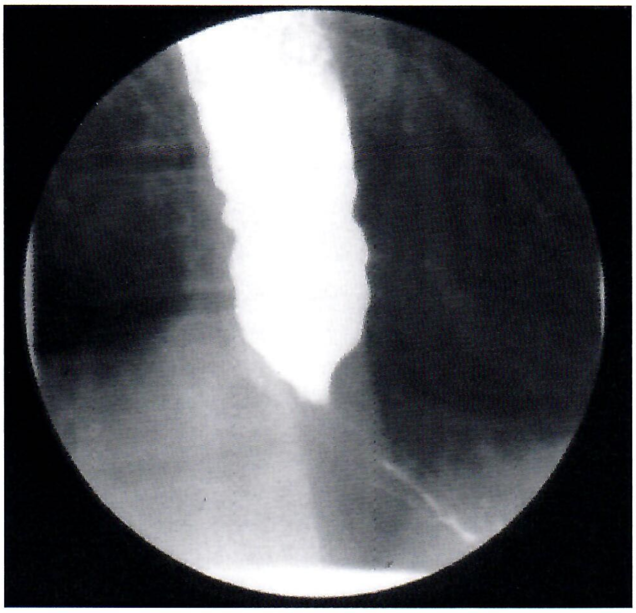

FIGURE 5. Barium esophagram showing the typical appearance of a dilated esophagus and "bird's beak" narrowing at the gastroesophageal junction in a patient with achalasia.

agents. Extrinsic compression from surgical procedures, such as fundoplication or bariatric surgery (gastric band), can also cause secondary achalasia.

There is a spectrum of achalasia-type disorders. Classic achalasia is characterized by a hypertonic LES and aperistalsis. Another subtype may include hypertonic LES, aperistalsis, and panesophageal pressurization (increased pressure of the entire esophageal body between the lower and upper esophageal sphincters).

The initial diagnostic test is barium esophagography, which shows dilation of the esophagus with narrowing at the gastroesophageal junction, known as a "bird's beak" (**Figure 5**). Upper endoscopy reveals retained food and saliva, no signs of mechanical obstruction or mass, and "tightness" at the gastroesophageal junction while the scope is advanced into the stomach. In classic achalasia, esophageal manometry shows incomplete LES relaxation and aperistalsis and confirms the diagnosis. Manometry may also detect evolving achalasia variants or spastic achalasia variants.

Pseudoachalasia results from malignant tumor infiltration or other secondary causes leading to myenteric plexus damage and can present similarly to achalasia. Unlike achalasia, pseudoachalasia has been associated with sudden weight loss later in life. Three clinical features suggest cancer as a cause of pseudoachalasia: short duration of dysphagia (<1 year), weight loss (>6.8 kg), and age older than 55 years. Suspected pseudoachalasia should be evaluated with CT, endoscopy, or endoscopic ultrasonography.

Treatment of achalasia includes endoscopic or surgical intervention with the goal of lowering LES pressure, which relieves symptoms. Medical therapy is uncommonly used.

Endoscopy with botulinum toxin injection into the LES inhibits acetylcholine release, relaxing the LES. However, after 1 year, only 40% of patients have continued symptom relief. Botulinum toxin injection can be repeated, but successive treatments are often less effective for symptom management. Pneumatic dilation is an effective nonsurgical therapy. Dilators ranging from 30 mm to 40 mm are used to disrupt the circular muscle. Clinical symptom relief ranges from 50% to 90%, and the most common complication is perforation.

Surgical treatment consists of laparoscopic myotomy of the circular muscle fibers. A partial fundoplication may also be done laparoscopically to prevent reflux symptoms after myotomy. Advantages of laparoscopic myotomy include the ability to address any hiatal hernia, if present, and perform a concurrent antireflux procedure. Peroral endoscopic myotomy (POEM) is a newer procedure that entails creation of an esophageal submucosal tunnel extending to the LES and then a myotomy. Advantages of POEM include the lack of skin incisions and ability to perform a longer myotomy, which may be beneficial in spastic achalasia. Disadvantages include risk for reflux. Choice of therapy depends on patient factors, type of disease, and available local expertise.

Medical therapy is reserved for poor candidates for endoscopic or surgical therapy. LES pressure can be reduced with medical therapy, including calcium channel blockers (nifedipine) or long-acting nitrates.

Patients with achalasia for more than 10 years have increased risk for squamous cell carcinoma and may benefit from surveillance endoscopy, but there are no established guidelines for frequency of surveillance.

Diffuse Esophageal Spasm and Jackhammer Esophagus

Spastic disorders of the esophagus may present with chest pain or dysphagia. Diffuse esophageal spasms are characterized by premature contractions, and the esophagus has a "corkscrew" (**Figure 6**) or "rosary bead" appearance on esophagography. Jackhammer esophagus occurs in patients with high-vigor peristaltic contractions.

Symptoms often respond to nitroglycerin, suggesting a flaw in esophageal nitric oxide production. Any GERD symptoms should be treated with a PPI. In patients without GERD symptoms, medical therapy with antidepressants (trazadone, imipramine) or a phosphodiesterase inhibitor (sildenafil) can relieve chest pain. Dysphagia may respond to calcium channel blockers. Botulinum toxin injection has alleviated dysphagia symptoms.

Hypotonic Motility Disorders

Hypotonic disorders of the esophagus are marked by lack of contractility and incomplete peristalsis. Patients may report GERD symptoms, which result from decreased LES pressure or dysphagia from incomplete peristalsis. In most cases, the cause of hypotonic esophageal disease is unknown. However, secondary causes include smooth-muscle relaxants, anticholinergic agents, estrogen, progesterone, connective

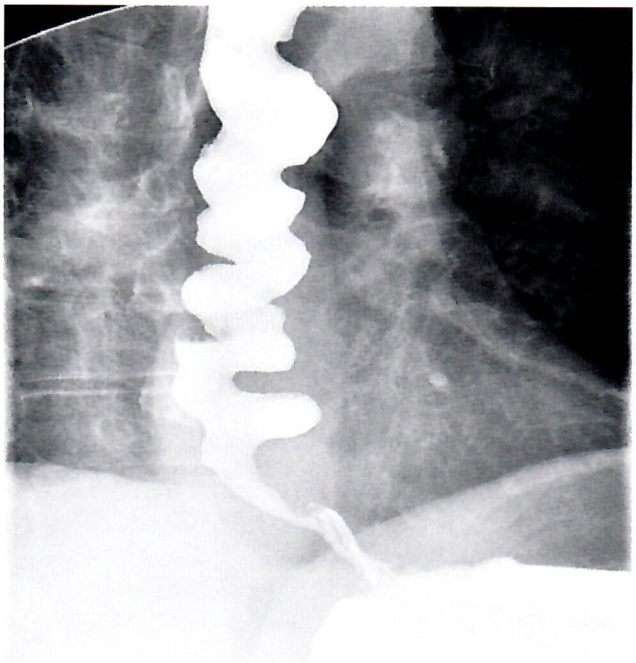

FIGURE 6. Findings of a "corkscrew" esophagus (caused by multiple simultaneous contractions) on esophagography are typical of diffuse esophageal spasm.

tissue disorders (e.g., systemic sclerosis), and pregnancy. Esophageal manometry shows weak nonperistaltic contractions in the distal esophagus. Findings can mimic those of achalasia.

Treatment includes lifestyle changes, such as eating upright and consuming liquid or semisolid rather than solid food. Medical therapy includes acid-reducing agents for GERD and low-dose antidepressants to reduce chest discomfort. Prokinetic agents (e.g., metoclopramide) are not recommended.

KEY POINTS

HVC
- In patients with symptoms of gastroesophageal reflux disease but without alarm features, an empiric trial of a proton pump inhibitor is the initial management.
- The diagnostic criteria for eosinophilic esophagitis are esophageal symptoms (most commonly dysphagia), esophageal biopsy specimens showing persistent eosinophil counts of 15/hpf or greater, and exclusion of other causes of eosinophilia.

HVC
- *Candida* esophagitis can be diagnosed clinically on the basis of compatible symptoms, such as dysphagia and oral candidiasis.
- Herpes simplex virus and cytomegalovirus esophagitis are seen in immunodeficient or immunosuppressed individuals; endoscopy with biopsy is needed to confirm the diagnosis.
- Treatments for achalasia include botulinum toxin injection, pneumatic dilation, and surgical myotomy; botulinum toxin injection is associated with high relapse rates.

Metaplastic and Neoplastic Disorders of the Esophagus

Barrett Esophagus

Epidemiology and Screening

Barrett esophagus is the replacement of the squamous epithelium with metaplastic columnar epithelium in the esophagus. It is a consequence of GERD, even in patients without clinical symptoms, and is a precursor lesion for esophageal cancer. Risk factors associated with Barrett esophagus include chronic GERD (for >5 years), age older than 50 years, male sex, white race, tobacco use, and obesity. Drinking alcohol is not associated with increased risk for Barrett esophagus, and wine consumption might be protective.

The annual cancer risks are 0.2% to 0.5% per year for Barrett esophagus without dysplasia, 0.7% per year for Barrett esophagus with low-grade dysplasia, and 7% per year for Barrett esophagus with high-grade dysplasia.

About 10% of patients with GERD are found to have Barrett esophagus on endoscopy. Evidence does not support routine screening for Barrett esophagus based on GERD symptoms for the general population. Studies suggest that individuals with multiple risk factors for esophageal carcinoma and chronic GERD might benefit from screening. Men older than 50 years with GERD symptoms for more than 5 years and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, intra-abdominal distribution of body fat, tobacco use) may benefit from screening endoscopy. Women generally do not require routine endoscopic screening for Barrett esophagus and should be selected for screening on a case-by-case basis.

Diagnosis and Management

Barrett esophagus is diagnosed by endoscopic findings (**Figure 7**) with biopsy, which are then confirmed by pathology showing specialized intestinal metaplasia with acid-mucin–containing goblet cells. Barrett esophagus is categorized by endoscopy measurements as short-segment (≤3 cm) or long-segment (>3 cm). Long segments are at a higher risk for cancer progression than are short segments.

Barrett esophagus progresses along a continuum: intestinal metaplasia, indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, intramucosal carcinoma, and, finally, invasive adenocarcinoma. The stage informs surveillance and treatment recommendations (**Table 4**).

In patients with Barrett esophagus, medical therapy should be used to treat reflux symptoms and to heal reflux esophagitis. No strong evidence suggests that antireflux surgery can prevent progression of Barrett esophagus to adenocarcinoma when compared with medical therapy with PPIs.

Endoscopy-based therapies for patients with confirmed dysplasia include endoscopic mucosal resection for all visible lesions and radiofrequency ablation; experience with other ablative methods, such as cryotherapy, is growing.

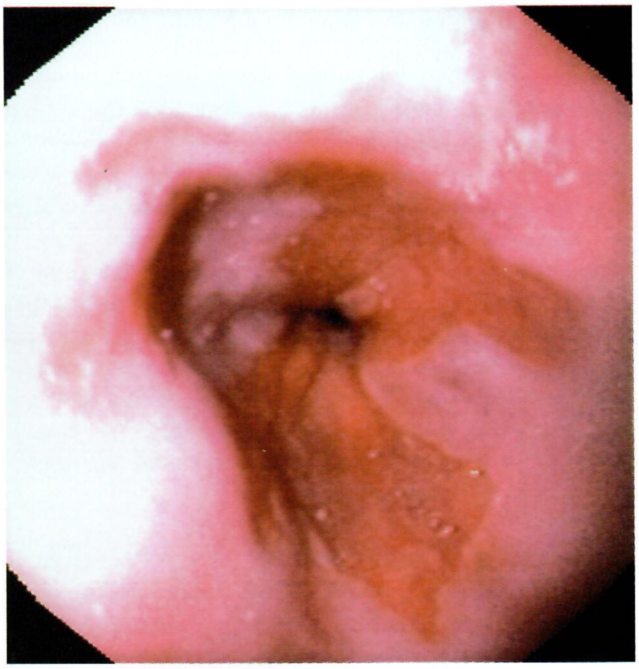

FIGURE 7. Upper endoscopic view of Barrett mucosa (salmon-colored) versus normal squamous mucosa (pink-colored).

Esophageal Carcinoma

Epidemiology

The global incidence of esophageal cancer varies widely; high-prevalence areas include Asia and southern and eastern Africa. The two types of esophageal carcinoma are squamous cell carcinoma and adenocarcinoma. Worldwide, squamous cell carcinoma makes up about 90% of all esophageal cancers; however, the incidence has been decreasing, whereas the incidence of adenocarcinoma has been rising. Esophageal cancer occurs in the fifth to seventh decades of life and is three to four times more common in men. In the United States, about 16,000 new cases are reported annually, with 15,000 deaths occurring in the same year. The overall 5-year survival rate ranges from 15% to 25%, depending on the cancer stage at initial presentation.

Risk Factors

Risk factors for adenocarcinoma include male sex, older age, GERD, Barrett esophagus, obesity, and tobacco use. Risk factors for squamous cell carcinoma include tobacco and alcohol use, caustic injury, achalasia, past thoracic radiation, nutritional deficiencies (zinc, selenium), poor socioeconomic status, poor oral hygiene, nonepidermolytic palmoplantar keratoderma (an autosomal dominant disorder associated with yellow wax-like hyperkeratosis on the palms and soles, also known as tylosis), human papillomavirus infection, and nitrosamine exposure.

Diagnosis and Staging

The most common initial presentation of esophageal carcinoma is dysphagia with solid foods, but asymptomatic individuals have been diagnosed according to surveillance endoscopic findings. Other symptoms include weight loss, anorexia, anemia (secondary to gastrointestinal bleeding), and chest pain. Upper endoscopy with biopsy is the preferred diagnostic test.

Squamous cell carcinoma is most commonly located in the proximal esophagus, and adenocarcinoma is usually found in the distal esophagus.

TNM staging is often done with endoscopic ultrasonography for locoregional disease and with CT and PET to identify metastatic disease. For treatment of esophageal carcinoma, see MKSAP 19 Oncology.

Superficial tumors that are limited to the mucosal lining (T1a), show no evidence of lymph node metastasis, and have low-risk features in terms of differentiation and lymphovascular invasion may be treated with endoscopic resection in an organ-sparing manner.

KEY POINTS

- Barrett esophagus is a precursor cancer lesion caused by long-standing gastroesophageal reflux disease (GERD).
- Routine screening for Barrett esophagus in patients with GERD symptoms is not recommended but should be considered in men older than 50 years with GERD symptoms for more than 5 years and additional risk factors.

(Continued)

TABLE 4. Practice Guidelines for Endoscopic Surveillance and Treatment of Barrett Esophagus

Dysplasia Grade	Recommendation
None	If no dysplasia is present, repeat upper endoscopy every 3 to 5 years
Indefinite	Start or adjust proton pump inhibitor therapy, then repeat endoscopy in 3 to 6 months
	If still present, then repeat endoscopy in 1 year
Low-grade	Confirmation by expert pathologist. Start or adjust proton pump inhibitor therapy. Repeat endoscopy in 3 to 6 months to rule out a visible lesion that should prompt resection; with confirmed low-grade dysplasia, endoscopic eradication therapy or annual surveillance endoscopy is an acceptable option
High-grade	Confirmation by expert pathologist
	Endoscopic eradication therapy is preferred

Data obtained from Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30-50; quiz 51. [PMID: 26526079] doi:10.1038/ajg.2015.322; and Sharma P, Shaheen NJ, Katzka D, et al. AGA clinical practice update on endoscopic treatment of Barrett's esophagus with dysplasia and/or early cancer: expert review. Gastroenterology. 2020;158:760-769. [PMID: 31730766] doi:10.1053/j.gastro.2019.09.051.

KEY POINTS ***(continued)***

- Patients with Barrett esophagus should receive proton pump inhibitor therapy; endoscopy-based ablation therapies are recommended for confirmed dysplasia.
- Dysphagia with solid foods is the most common presenting symptom of esophageal carcinoma.

Disorders of the Stomach and Duodenum

Dyspepsia

Clinical Features

Dyspepsia is a term to describe epigastric pain. Associated symptoms can include early satiety, epigastric burning, nausea, and postprandial symptoms (e.g., pain, fullness, bloating, or belching). Heartburn may be present but is not a primary symptom; it may indicate coexisting gastroesophageal reflux. Recurrent vomiting should also raise concern for other conditions.

The list of possible organic causes of dyspepsia is extensive (**Table 5**); the most common are peptic ulcer disease and gastroesophageal reflux disease (20% of patients with erosive esophagitis report dyspepsia). If no structural, organic, or metabolic cause of dyspepsia symptoms is identified after evaluation, the term *functional dyspepsia* applies.

Functional dyspepsia represents a heterogeneous group of gastrointestinal disorders predominated by one or more upper gastrointestinal symptoms. Diagnostic criteria for functional dyspepsia are shown in **Table 6**. Functional dyspepsia is further categorized into postprandial distress syndrome if the predominant symptoms are meal-induced (**Table 7**) or epigastric pain syndrome if the predominant symptoms are epigastric pain and/or burning (**Table 8**).

TABLE 5. Structural and Other Causes of Dyspepsia

Category	Clinical Examples
Gastroesophageal	Gastroesophageal reflux disease, peptic ulcer disease, *Helicobacter pylori* gastritis, gastric cancer/lymphoma, gastric amyloidosis, Ménétrier disease, gastroparesis
Small bowel	Celiac disease, Crohn disease
Pancreatic	Pancreatitis, pancreatic cancer
Infectious	*Giardia lamblia*, *Strongyloides stercoralis*, tuberculosis, syphilis
Common medications	NSAIDs, aspirin, iron, antibiotics (erythromycin, ampicillin), narcotics, estrogens and oral contraceptives, theophylline, levodopa, digitalis
Other systemic conditions	Coronary artery disease, kidney disease, thyroid dysfunction, adrenal insufficiency, hyperparathyroidism, pregnancy

Evaluation and Management

Testing for dyspepsia should be based on patient age, symptom severity, and risk for gastric cancer. Upper endoscopy is commonly performed to exclude upper gastrointestinal neoplasia; however, it is invasive and costly. Given the low incidence of malignancy and consideration for cost effectiveness in the

TABLE 6. Rome 4 Diagnostic Criteria for Functional Dyspepsia

One or more of the following[a]:

Bothersome postprandial fullness

Bothersome early satiation

Bothersome epigastric pain

Bothersome epigastric burning

No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reproduced with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

TABLE 7. Rome 4 Diagnostic Criteria for Postprandial Distress Syndrome

Criteria[a]	Supportive Remarks
Must include one or both of the following at least 3 days per week:	Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
Bothersome postprandial fullness (i.e., severe enough to affect usual activities)	Vomiting warrants consideration of another disorder
	Heartburn is not a dyspeptic symptom but may often coexist
Bothersome early satiation (i.e., severe enough to prevent finishing a regular-sized meal)	Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)	Other individual digestive symptoms or groups of symptoms, such as from gastroesophageal reflux disease and irritable bowel syndrome, may coexist

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reproduced with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

TABLE 8. Rome 4 Diagnostic Criteria for Epigastric Pain Syndrome

Criteria[a]	Supportive Remarks
Must include the following symptoms at least 1 day per week: Bothersome epigastric pain and/or burning (i.e., severe enough to affect usual activities) No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)	Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting Postprandial epigastric bloating, belching, and nausea can also be present Persistent vomiting suggests another disorder Heartburn is not a dyspeptic symptom but may often coexist The pain does not fulfill biliary pain criteria Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia Other individual digestive symptoms or groups of symptoms, such as from gastroesophageal reflux disease and irritable bowel syndrome, may coexist

[a] Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reproduced with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

evaluation of dyspepsia in younger adults, the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) have jointly recommended routine use of upper endoscopy only in patients age 60 years and older. The ACG/CAG guidelines recommend against routine use of upper endoscopy in patients younger than 60 years with dyspepsia, even in most patients with alarm features (weight loss, anemia, dysphagia, and vomiting) because these features poorly predict structural pathology, such as malignancy, peptic ulcer disease, or esophagitis. Endoscopy may be considered in younger patients at higher risk for malignancy, such as those with multiple or severe alarm features; those who have emigrated from regions with a high prevalence of malignancy (Asia, Russia, and South America); or those with a positive family history of gastric malignancy.

For patients younger than 60 years with dyspepsia symptoms, the ACG/CAG guidelines recommend noninvasive testing for *Helicobacter pylori*. Other testing, such as routine laboratory tests, screening for celiac disease, abdominal imaging, or gastric emptying, should be considered on an individual basis.

Management of dyspepsia is directed at treating the cause. Patients who test positive for *H. pylori* should receive eradication therapy. If *H. pylori* results are negative or *H. pylori* eradication does not relieve the dyspepsia, an empiric trial of a proton pump inhibitor (PPI) should be pursued. Patients diagnosed with functional dyspepsia can be treated with a variety of interventions (**Figure 8**).

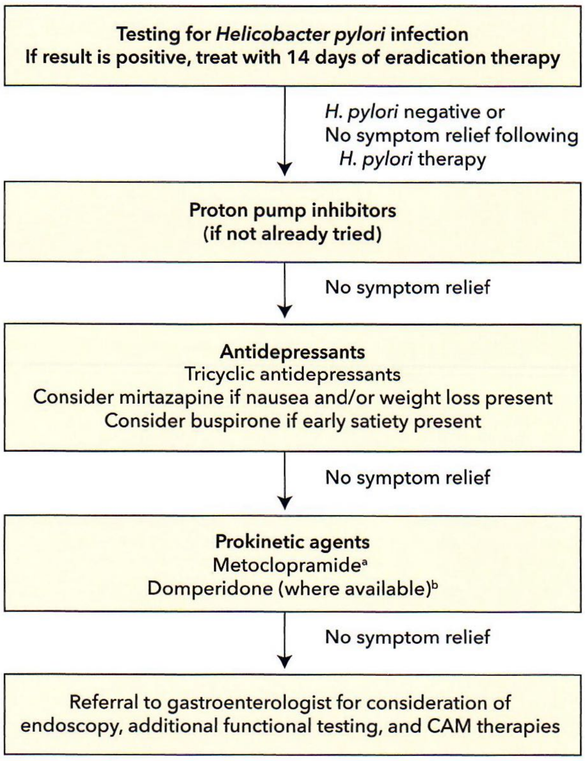
Testing for Helicobacter pylori infection
If result is positive, treat with 14 days of eradication therapy
H. pylori negative or
No symptom relief following
H. pylori therapy
Proton pump inhibitors
(if not already tried)
No symptom relief
Antidepressants
Tricyclic antidepressants
Consider mirtazapine if nausea and/or weight loss present
Consider buspirone if early satiety present
No symptom relief
Prokinetic agents
Metoclopramide[a]
Domperidone (where available)[b]
No symptom relief
Referral to gastroenterologist for consideration of
endoscopy, additional functional testing, and CAM therapies

FIGURE 8. Treatment algorithm for functional dyspepsia.

CAM = complementary and alternative medicine.

[a] Avoid metoclopramide treatment longer than 12 weeks because of the increased risk for tardive dyskinesia with longer-term use that is often irreversible.

[b] Increased risk for serious ventricular arrhythmias or sudden cardiac death, particularly with doses greater than 30 mg or when used in patients older than age 60 years. Use the lowest possible dose for the shortest duration necessary. ECGs should be obtained at baseline and periodically thereafter to evaluate the QTc interval. Requires Investigational New Drug Application in the United States.

KEY POINTS

- For patients with dyspepsia, routine upper endoscopy to exclude malignancy is reserved for patients age 60 years and older. **HVC**
- Upper endoscopy is not necessary in most patients with dyspepsia younger than 60 years, even in the presence of alarm symptoms. **HVC**
- Patients younger than 60 years with dyspepsia symptoms should be tested and, if results are positive, treated for *Helicobacter pylori* infection. **HVC**

Peptic Ulcer Disease

Clinical Features, Diagnosis, and Complications

The most frequently reported symptom of peptic ulcer disease (PUD) is epigastric pain, often described as worse during fasting and improved with eating or use of antacid or antisecretory therapy. Pain may be accompanied by early satiety, abdominal bloating, nausea, belching, or heartburn. Epigastric pain may be minimal or absent in elderly patients, immunosuppressed patients, and patients receiving long-term NSAID therapy.

NSAIDs and *H. pylori* infection are the most common causes of PUD, although idiopathic (NSAID-negative, *H. pylori*–negative) PUD is increasingly visible as a cause in the United States as the incidence of *H. pylori* infection falls. The causes of idiopathic PUD remain unclear; however, cocaine, methamphetamine, bisphosphonates, selective serotonin reuptake inhibitors, smoking, excessive alcohol consumption, and stress have been implicated. Rare causes of PUD include gastrinoma (Zollinger-Ellison syndrome), systemic mastocytosis, α_1-antitrypsin deficiency, COPD, chronic kidney disease, gastric cancer, gastric lymphoma, Crohn disease, eosinophilic gastroenteritis, herpes simplex virus, and cytomegalovirus (in immunocompromised patients).

PUD is most often diagnosed by upper endoscopy.

Complications of PUD include bleeding, perforation, and obstruction. Overt bleeding presents with melena, hematemesis, and/or hematochezia, whereas obscure bleeding may present with iron deficiency anemia and/or stool that is positive for occult blood. Perforation typically presents with sudden, severe epigastric pain that can become more generalized along with peritoneal findings. Abdominal CT is the diagnostic study of choice for suspected perforating PUD (sensitivity, 98%). Symptoms associated with obstruction may include vomiting, early satiety, abdominal distention, and weight loss.

Management

Following confirmation of uncomplicated PUD, a once-daily PPI should be initiated and any agent causing PUD (such as an NSAID) should be discontinued. *H. pylori* infection should be treated if identified and eradication confirmed after treatment. When results of tests for *H. pylori* completed in the acute setting are negative, testing should be repeated after discharge.

Upper endoscopy should be performed within 24 hours in patients with acute upper gastrointestinal bleeding. In patients with bleeding PUD, factors that increase risk for recurrent bleeding and/or death include tachycardia, hypotension, age older than 60 years, hemoglobin level less than 7 g/dL (70 g/L) (8 g/dL [80 g/L] in patients with cardiovascular disease), and comorbid illness. Interventions to address modifiable risks should be pursued before upper endoscopy. Nasogastric tube placement is not required before upper endoscopy. Use of PPIs before upper endoscopy may improve the endoscopic appearance of ulcer and reduce the need for endoscopic therapy.

For bleeding PUD related to aspirin use for secondary cardiovascular prevention, aspirin should be restarted 1 to 7 days after initiation of PPI and cessation of bleeding. PPI therapy can be discontinued after confirmation of *H. pylori* eradication in patients with *H. pylori*–associated bleeding PUD. NSAIDs should be discontinued in patients with NSAID-induced bleeding PUD. If there is no effective alternative to NSAIDs, a selective cyclooxygenase-2 inhibitor plus a once-daily PPI should be used. Patients with idiopathic ulcers that have bled should receive once-daily PPI therapy indefinitely because of the substantial risk for rebleeding.

Repeat upper endoscopy to verify ulcer resolution should be reserved for patients who have persistent symptoms after 8 to 12 weeks of therapy, have ulcers of unknown cause, or did not undergo gastric ulcer biopsy during initial upper endoscopy.

Perforated PUD is a surgical emergency, with a mortality rate of up to 30%; older age, comorbidity, and delayed surgery increase risk. Prompt identification, urgent surgical intervention, and proper preoperative and postoperative management of sepsis are essential. The cause of PUD (*H. pylori* and/or NSAIDs) should be addressed, and postoperative upper endoscopy to rule out gastric cancer should be considered.

Patients with gastric outlet obstruction from inflammation or scarring at the pylorus or proximal duodenum should have biopsy at the time of diagnosis to exclude malignancy. For mild symptoms, PPI therapy, treatment of *H. pylori* infection (if identified), and/or cessation of NSAIDs may be effective. For severe or persistent symptoms, endoscopic dilation should be pursued, with surgery reserved for persistent obstruction following repeated attempts at endoscopic dilation.

KEY POINTS

- NSAIDs and *Helicobacter pylori* infection are the most common causes of peptic ulcer disease.
- For bleeding peptic ulcer disease related to aspirin use for secondary cardiovascular prevention, aspirin should be restarted 1 to 7 days after initiation of PPI and cessation of bleeding.
- NSAIDs should be discontinued in patients with NSAID-induced bleeding peptic ulcer disease; if there is no effective alternative to NSAIDs, a selective cyclooxygenase-2 inhibitor plus a once-daily PPI should be used.
- Patients with idiopathic ulcers that have bled should receive once-daily PPI therapy indefinitely because of the substantial risk for rebleeding.
- Repeat upper endoscopy to verify ulcer resolution is reserved for patients who have persistent symptoms after 8 to 12 weeks of therapy, have ulcers of unknown cause, or did not undergo gastric ulcer biopsy during the initial upper endoscopy. **HVC**

Helicobacter pylori Infection

Indications for Testing

Indications for *H. pylori* testing include active PUD, history of PUD without documented cure of *H. pylori* infection, gastric mucosa–associated lymphoid tissue lymphoma, or history of endoscopic resection of early gastric cancer. Other conditions in which *H. pylori* testing should be considered include dyspepsia, before long-term low-dose aspirin or NSAID use, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura in adults. Routine testing for *H. pylori* is not indicated in patients with typical gastroesophageal reflux disease symptoms, lymphocytic gastritis, hyperplastic gastric polyps, or hyperemesis gravidarum or in asymptomatic individuals with a family history of gastric cancer.

Diagnosis

H. pylori infection can be diagnosed with gastric biopsies during upper endoscopy or noninvasively by ^{13}C-urea breath, stool antigen, or serologic testing. The ^{13}C-urea breath test and the monoclonal stool antigen test are preferred noninvasive tests because sensitivity and specificity both exceed 95% for active infection. Serologic testing for IgG antibodies against *H. pylori* is the cheapest and most convenient method; however, it cannot distinguish between active and previous infection. Although the negative predictive value of serologic testing is reasonably high, a positive serologic result in a population with low prevalence of *H. pylori* infection, such as in the United States, may require confirmation with the ^{13}C-urea breath test, stool antigen test, or gastric biopsy. Serologic testing is most useful as an adjunct test in patients with bleeding PUD because of the decreased sensitivity of biopsy in acute bleeding. Conditions that lower *H. pylori* density, such as PPI use, recent antibiotic use, atrophic gastritis, intestinal metaplasia, or mucosa-associated lymphoid tissue lymphoma, can result in false-negative results on the noninvasive studies. Upper endoscopy that is done to evaluate dyspepsia should include gastric biopsy for *H. pylori* testing.

Treatment

Any patient with a test result positive for active infection requires treatment with the goal of *H. pylori* eradication. The first course of treatment offers the best chance of eradication and should be carefully chosen. Several first-line treatments are available, with the choice based on resistance patterns of *H. pylori*, previous antibiotic use by the patient, and antibiotic allergies (**Table 9**). In most cases, duration of therapy is 14 days. When treatment fails, second-line therapy should last a

TABLE 9. First-Line Treatment Options for *Helicobacter pylori* Infection

Treatment Regimen	Duration of Therapy	Clinical Indicators
PPI, standard[a] or double dose twice daily (esomeprazole, once daily only) Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	*H. pylori* clarithromycin resistance is known to be <15% No history of macrolide exposure for any reason
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Metronidazole, 500 mg three times daily	14 days	*H. pylori* clarithromycin resistance is known to be <15% No history of macrolide exposure for any reason Penicillin allergy
PPI, standard dose twice daily Bismuth subcitrate, 120-300 mg or subsalicylate, 300 mg four times daily Tetracycline, 500 mg four times daily Metronidazole, 250 mg four times daily or 500 mg three times daily	10-14 days	Previous macrolide exposure Penicillin allergy
PPI, standard dose twice daily Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily Metronidazole or tinidazole, 500 mg twice daily	10-14 days	May be an alternative to standard clarithromycin triple therapy Not validated in North America
PPI, standard dose twice daily Levofloxacin, 500 mg once daily Amoxicillin, 1 g twice daily	10-14 days	May be an alternative to standard clarithromycin triple therapy Not validated in North America

PPI = proton pump inhibitor.

[a] Standard-dose PPIs: esomeprazole, 40 mg; lansoprazole, 30 mg; omeprazole, 20 mg; pantoprazole, 40 mg; rabeprazole, 20 mg.

Adapted with permission from Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563.

TABLE 10. Second-Line Treatment for *Helicobacter pylori* Infection After Failure of Initial Treatment

Treatment Regimen	Duration of Therapy	Clinical Indicators
PPI, standard dose twice daily[a] Bismuth subcitrate, 120-300 mg, or subsalicylate, 300 mg four times daily Tetracycline, 500 mg four times daily Metronidazole, 500 mg three or four times daily	14 days	Failure of clarithromycin-based or levofloxacin-based therapy
PPI, standard dose twice daily Levofloxacin, 500 mg once daily Amoxicillin, 1 g twice daily	14 days	Failure of bismuth-based or clarithromycin-based therapy
PPI, standard dose twice daily[a] Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily Metronidazole or tinidazole, 500 mg twice or three times daily	10-14 days	Failure of bismuth-based therapy

PPI = proton pump inhibitor.

[a] Standard-dose PPIs: esomeprazole, 40 mg; lansoprazole, 30 mg; omeprazole, 20 mg; pantoprazole, 40 mg; rabeprazole, 20 mg.

Adapted with permission from Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563.

minimum of 14 days, ideally with antibiotics different from those used for initial treatment (**Table 10**).

Eradication Testing

No sooner than 4 weeks after completion of eradication therapy and cessation of PPI therapy (if possible), eradication of *H. pylori* should be tested by using a ^{13}C-urea breath test, fecal antigen test, or gastric biopsy performed during upper endoscopy. Serologic testing is not used to confirm *H. pylori* eradication because results can remain positive following *H. pylori* eradication.

KEY POINTS

- Gastric biopsies during upper endoscopy or noninvasive testing methods, including ^{13}C-urea breath and stool antigen tests, can confirm active *H. pylori* infection; negative serologic results can exclude infection, but a positive serologic result may require confirmation.
- Treatment regimens for *H. pylori* consist of a minimum of three agents, including two antimicrobial agents and one antisecretory agent; treatment duration is 14 days in most cases.
- Eradication of *H. pylori* is tested with a ^{13}C-urea breath test, fecal antigen test, or gastric biopsy performed during upper endoscopy no sooner than 4 weeks after completion of eradication therapy and cessation of PPI therapy (if possible).

Miscellaneous Gastropathy

Erosive Gastropathy

Erosive gastropathy can result from exposure to medications and toxins, including NSAIDs, iron, and alcohol. Ischemia and portal hypertension are additional causes. Although erosive gastropathy may result in gastrointestinal bleeding, it rarely causes clinically significant bleeding.

Atrophic Gastritis

Chronic atrophic gastritis can present as environmental metaplastic atrophic gastritis, also called *multifocal atrophic gastritis*, or as autoimmune atrophic gastritis. Environmental metaplastic atrophic gastritis is the result of *H. pylori* infection and typically lessens after *H. pylori* eradication. Autoimmune atrophic gastritis is caused by formation of autoantibody to parietal cell antigens and is commonly associated with pernicious anemia. The achlorhydria from chronic atrophic gastritis can lead to iron deficiency, small intestinal bacterial overgrowth, and enteric infections. The hypergastrinemia associated with autoimmune atrophic gastritis can promote development of gastric neuroendocrine tumors. Goals of therapy for autoimmune atrophic gastritis include prevention of pernicious anemia and iron deficiency with vitamin B_{12} supplementation and iron replacement along with surveillance for gastric neoplasm. See MKSAP 19 Hematology for further discussion of pernicious anemia in the setting of autoimmune gastritis. Screening upper endoscopy with gastric biopsy is recommended for patients with pernicious anemia. Otherwise, there are no universally accepted surveillance protocols for gastric neoplasm in chronic atrophic gastritis, and endoscopic surveillance should be considered on an individual basis. Annual endoscopy is generally not necessary.

Gastric Intestinal Metaplasia

Gastric intestinal metaplasia is a preneoplastic gastropathy frequently arising from chronic inflammation associated with *H. pylori* infection. As such, patients with gastric intestinal metaplasia should be tested for *H. pylori* and then treated if the infection is identified. Other causes of chronic inflammation, including other gastric infections, chemical agents, and autoimmune disease, may also promote progression to gastric intestinal metaplasia. No conclusive evidence shows that long-term PPI use promotes development of intestinal metaplasia. Gastric intestinal metaplasia is believed to be an intermediary stage in the multistage progression from chronic atrophic gastritis to gastric adenocarcinoma. If metaplasia is secondary to *H. pylori* infection, eradication therapy may decrease progression to gastric adenocarcinoma. Given the rarity of gastric adenocarcinoma in the United States, current guidelines recommend against the routine use of surveillance endoscopy in gastric intestinal metaplasia. Surveillance endoscopy can be considered in patients at increased risk (such as those with complete or extensive gastric intestinal metaplasia on endoscopy; those with a family history of gastric cancer; persons from racial/ethnic minority groups; or those who have emigrated from East Asia, Russia, or South America).

Eosinophilic Gastritis

Eosinophilic gastritis is a rare gastropathy characterized by infiltration of eosinophils in the gastric mucosa. Secondary causes of eosinophilia should first be excluded, including parasitic and bacterial infections of the stomach, inflammatory bowel disease, hypereosinophilic syndrome, myeloproliferative disorders, polyarteritis nodosa, allergic vasculitis, scleroderma, drug injury, and drug hypersensitivity. The cause of primary eosinophilic gastritis is unknown but is believed to be an allergic process. Symptoms vary widely based on depth of eosinophilia and other gastrointestinal tract involvement. Treatment includes avoidance of food allergens, elemental diets, and/or glucocorticoids.

Lymphocytic Gastritis

Lymphocytic gastritis is a rare gastropathy typically presenting with nonspecific dyspeptic symptoms and a normal-appearing stomach on endoscopy. On occasion, the stomach may have thickened folds covered by small nodules and aphthous ulceration. Celiac disease is the most common cause of lymphocytic gastritis. Other causes include HIV infection, Crohn disease, common variable immunodeficiency, and, rarely, *H. pylori* infection.

KEY POINTS

- Autoimmune atrophic gastritis is associated with pernicious anemia, iron deficiency, small intestinal bacterial overgrowth, and gastric carcinoid.
- Management of autoimmune atrophic gastritis includes prevention of pernicious anemia and iron deficiency with vitamin B_{12} supplementation and iron replacement along with surveillance for gastric neoplasm.
- *Helicobacter pylori* is associated with upper gastrointestinal conditions other than peptic ulcer disease, including environmental metaplastic atrophic gastritis, gastric intestinal metaplasia, and, rarely, lymphocytic gastritis.

TABLE 11. Risk Factors for NSAID-Related Upper Gastrointestinal Complications

History of upper gastrointestinal bleeding
History of peptic ulcer disease
Helicobacter pylori infection
Age >65 years
Hemodialysis or peritoneal dialysis
Use of high-dose or multiple NSAIDs
Concomitant use of aspirin (even low-dose), nonaspirin antiplatelet agents, anticoagulants, oral glucocorticoids, or selective serotonin reuptake inhibitors

Gastrointestinal Complications of NSAIDs

Epidemiology and Risk Factors

Upper gastrointestinal complications can occur with short- or long-term NSAID use and are dose dependent, with a linear increase in incidence over time. Nearly 1% to 2% of patients taking long-term NSAID therapy experience a clinically significant upper gastrointestinal event (bleeding ulcer, perforation, or obstruction) annually. The rate of upper gastrointestinal adverse events rises to 14% for elderly NSAID users. The greatest risk factor for NSAID-related upper gastrointestinal complication is a history of gastrointestinal bleeding. Risk factors are listed in **Table 11**.

Use of low-dose aspirin for cardioprophylaxis is associated with a twofold to fourfold increase in risk for upper gastrointestinal complications, including bleeding ulcer, perforation, and obstruction. Use of enteric-coated aspirin does not lower this risk, and an increase in aspirin dosage is associated with an increased risk for upper gastrointestinal complications. See MKSAP 19 General Internal Medicine 2 for discussion of indications for primary and secondary prevention of cardiovascular disease with aspirin.

Prevention of NSAID-Induced Injury

Prevention of NSAID-related upper gastrointestinal adverse events includes avoiding NSAIDs; addressing modifiable risk factors; coadministering gastroprotective agents, such as PPIs, misoprostol, or H_2-blockers; or using a selective cyclooxygenase (COX)-2 inhibitor. PPIs are the preferred gastroprotective agent for the treatment and prophylaxis of NSAID-related (including aspirin-related) upper gastrointestinal complications and are superior to H_2-blockers for preventing PUD and bleeding related to low-dose aspirin use. Misoprostol may be used instead of PPIs in patients intolerant of or unwilling to take PPIs. However, side effects of misoprostol, such as diarrhea, abdominal discomfort, and nausea, can be limiting, and the drug is contraindicated in pregnancy.

Selective COX-2 inhibitors are associated with decreased risk for gastrointestinal toxicity compared with NSAIDs, although the risk is still elevated. When coadministered with aspirin, however, a selective COX-2 inhibitor provides no advantage over an NSAID in preventing an upper gastrointestinal adverse event. Given the increased risk for PUD with concomitant use of an NSAID or selective COX-2 inhibitor with low-dose aspirin, at-risk individuals should receive gastroprotective therapy. Compared to an NSAID plus a PPI in patients at high risk, a selective COX-2 inhibitor plus a PPI offers a lower risk for perforation, obstruction, and bleeding as well as for NSAID and COX-2 withdrawal due to gastrointestinal adverse events.

After an NSAID-induced bleeding peptic ulcer, the safest strategy is avoidance of future NSAID use. If an NSAID must be used, the combination of a selective COX-2 inhibitor plus a PPI provides the best gastrointestinal protection to prevent rebleeding.

KEY POINTS

- Upper gastrointestinal complications, such as bleeding, are common with use of NSAIDs (both short- and long-term) and low-dose aspirin.
- Proton pump inhibitors are the preferred agent for preventing and treating NSAID-related (including aspirin-related) upper gastrointestinal complications.
- In individuals with high risk for gastrointestinal complications, including those with previous NSAID-induced gastrointestinal bleeding, the combination of a selective cyclooxygenase-2 inhibitor plus a proton pump inhibitor provides the best gastrointestinal protection if avoidance of NSAIDs is not possible.

Gastroparesis

Presentation

Gastroparesis is a heterogeneous clinical syndrome characterized by the presence of specific symptoms, absence of mechanical outlet obstruction, and objective evidence of delay in gastric emptying into the duodenum. The most common symptoms, in order of prevalence, are nausea (90%), vomiting (84%), upper abdominal pain (72%), and early satiety (60%). Other symptoms may include abdominal fullness and bloating. Symptoms may be chronic or persistent or may occur intermittently. More severe cases may involve weight loss and evidence of malnutrition and/or dehydration. A viral prodrome, such as gastroenteritis or respiratory infection before symptom onset, may suggest postviral gastroparesis, a condition that can resolve over time. Gastroparesis has a variety of causes (**Table 12**).

TABLE 12. Causes of Gastroparesis

Common Causes
Diabetes mellitus (40% in long-standing type 1 diabetes mellitus, 20% in type 2 diabetes mellitus)
Postsurgical (e.g., Nissen fundoplication, bariatric surgery, pancreatic surgery)
Idiopathic (e.g., postviral)
Infrequent Causes
Connective tissue disease (e.g., systemic sclerosis)
Neurologic disease (e.g., Parkinson disease)
Eating disorders
Hypothyroidism
Amyloidosis
Paraneoplastic syndromes (e.g., small cell lung cancer)
Mesenteric ischemia
Medications (e.g., opiates, anticholinergic agents)

Diagnostic Testing

The first study to evaluate suspected gastroparesis is upper endoscopy to exclude gastric outlet obstruction. Once a structural cause for symptoms has been excluded, an objective test to assess gastric emptying is performed: gastric scintigraphy, wireless motility capsule, or gastric emptying carbon breath test using ^{13}C-labeled *Spirulina platensis* (**Table 13**). Gastric scintigraphy is the most commonly used, but the optimal duration of this study is 4 hours. Narcotic and anticholinergic agents must be stopped at least 72 hours before a gastric emptying study. Once delayed emptying is objectively confirmed, additional testing may be required to determine the cause of the gastroparesis.

Management

Symptom severity does not correlate with severity of delayed gastric emptying, particularly with regard to abdominal bloating and epigastric pain. This suggests that gastroparesis is not simply a motility disorder but also a disorder of altered sensation. Initial management includes correcting dehydration and electrolyte abnormalities along with nutritional support if needed. Initial dietary intervention should consist of small, frequent meals that are low in fat and soluble fiber. Referral to a dietitian may be beneficial. In diabetic gastroparesis, poor glycemic control (blood glucose level >200 mg/dL [11.1 mmol/L]) can worsen symptoms as well as gastric emptying, and tight glycemic control is the most important element of treatment.

Pharmacologic therapy is used to improve gastric emptying and treat symptoms. Metoclopramide is the only prokinetic approved in the United States for treatment of gastroparesis. To minimize the significant risk for neurologic side effects (dystonia, parkinsonian movements, tardive dyskinesia), the lowest effective dose should be used. Therapy must be stopped immediately if neurologic side effects develop.

Erythromycin improves gastric emptying, but use should be limited to treatment of flares or short-term use (2 to 3 weeks) because of risk for tachyphylaxis.

Antiemetics and centrally acting modulators, including tricyclic antidepressants and mirtazapine, can also relieve symptoms but have no beneficial effect on gastric emptying.

TABLE 13. Diagnostic Tests Assessing Gastric Emptying

Test	Advantages	Disadvantages	Clinical Pearls
Gastric scintigraphy	Considered the gold standard	Radiation exposure (technetium radiolabeled meal) Requires specially trained personnel Cost	Study lasting 4 hours is most accurate Assesses solid emptying (liquid emptying is less accurate) Blood glucose should be <275 mg/dL (15.3 mmol/L)
Wireless motility capsule	Can also assess small bowel, colon, and whole gut transit No radiation Ambulatory study	Cost Can't be used with pacemaker or implantable cardioverter-defibrillator Risk for capsule retention	Consider in patient suspected of having global motility problem Stop antisecretory agents because study relies on measurement of pH
Gastric emptying carbon breath test	No radiation	Avoid in setting of *Spirulina* supplementation or egg, milk, or wheat hypersensitivity	Accuracy adversely affected by conditions altering endogenous CO_2 production Avoid physical activity during testing Avoid in patients with small-bowel malabsorption, pancreatic insufficiency, COPD, chronic heart failure, or advanced liver disease

Interventional therapy, such as enteral feeding via jejunostomy, gastric stimulator placement, gastric peroral endoscopic myotomy, pyloroplasty, and subtotal or total gastrectomy, can be considered in patients who do not respond to dietary and pharmacologic therapy.

KEY POINTS

- After gastric outlet obstruction is excluded by upper endoscopy, patients suspected of gastroparesis should undergo an objective test of gastric emptying, typically gastric scintigraphy.
- Initial management of gastroparesis includes correcting dehydration and electrolyte abnormalities; nutritional support; small, frequent meals that are low in fat and soluble fiber; and, in patients with diabetes mellitus, improved glycemic control.
- Metoclopramide is a prokinetic drug that improves gastric emptying but is associated with dystonia, tardive dyskinesia, and parkinsonism.

Gastric Polyps and Subepithelial Lesions

Gastric Polyps

Polyps in the stomach include fundic gland polyps, hyperplastic polyps, and adenomas. All gastric polyps should be biopsied to determine polyp histology. Fundic gland polyps and hyperplastic polyps account for 70% to 90% of stomach polyps. Fundic gland polyps have no potential for malignancy and are common with PPI use. Multiple fundic gland polyps are also found in patients with familial adenomatous polyposis.

Hyperplastic polyps of the stomach are thought to have malignant potential, with 5% to 19% harboring dysplasia or malignancy. Risk factors for malignant potential of hyperplastic polyps include size greater than 1 cm and pedunculated morphology. All hyperplastic polyps greater than 0.5 to 1.0 cm should be resected.

Adenomas in the stomach can be sporadic or associated with hereditary syndromes, including familial adenomatous polyposis and Lynch syndrome. Those in the stomach should be resected and endoscopic surveillance should be performed 1 year after resection and then every 3 to 5 years thereafter.

Gastric Subepithelial Lesions

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the stomach. GISTs may present with symptoms, such as bleeding or abdominal pain, but are also found incidentally. Endoscopic ultrasonography is the best diagnostic modality for evaluation of a GIST. High-risk features on endoscopic ultrasonography include size greater than 2 cm, lobulated or irregular borders, invasion into adjacent structures, and heterogeneity. A GIST can be biopsied, but the high-risk endoscopic features are better predictors of malignant potential. Treatment consists of surgical or endoscopic excision if the GIST is symptomatic or high-risk features are present. For GISTs without high-risk features, yearly endoscopic surveillance is indicated. See MKSAP 19 Oncology for staging and treatment of GISTs.

Gastrointestinal Neuroendocrine Tumors

Neuroendocrine tumors (NETs; formerly called carcinoid tumors) are well-differentiated lesions originating in the digestive tract, lungs, or, rarely, kidneys or ovaries. NETs can be encountered throughout the gastrointestinal tract, including the stomach. They may present symptomatically or may be found incidentally. These tumors are usually sporadic but can be seen in the setting of Zollinger-Ellison syndrome; atrophic gastritis; and rare syndromes, such as multiple endocrine neoplasia type 1 and neurofibromatosis type 1. NETs are classified by size, number, and anatomic distribution. Management of gastrointestinal NETs includes endoscopic surveillance for lesions smaller than 1 cm, especially when multiple lesions are present. Endoscopic or surgical excision is indicated for gastrointestinal NETs with high-risk features, such as solitary lesions not found in the setting of atrophic gastritis or Zollinger-Ellison syndrome. See MKSAP 19 Oncology for treatment of gastrointestinal NETs.

KEY POINTS

- Polyps in the stomach include fundic gland polyps, which have no malignant potential; polyps with malignant potential, including hyperplastic polyps, and adenomas should be resected.
- Gastrointestinal stromal tumors should be evaluated with endoscopic ultrasonography and excised if symptoms or high-risk features are present.
- Neuroendocrine tumors are usually sporadic but can be seen in the setting of Zollinger-Ellison syndrome; atrophic gastritis; and rare syndromes, such as multiple endocrine neoplasia type 1 and neurofibromatosis type 1.

Gastric Adenocarcinoma

Epidemiology and Risk Factors

Stomach adenocarcinoma has an incidence of 6.6 in 100,000 persons and a mortality of 3.1 per 100,000 persons in the United States. Rates have steadily decreased since the 1990s. The two types of gastric cancer are intestinal-type, which is more common, and diffuse-type. *H. pylori* is a recognized risk factor for both types and is the primary nongenetic risk factor for gastric cancer. Other risk factors primarily associated with intestinal-type gastric adenocarcinoma include male sex; ethnicity (incidence is highest in persons of Asian and Pacific Island descent, and mortality is highest in non-Hispanic white persons); geography (the highest rates worldwide occur in Asia, Eastern Europe, and Central and South America); a diet high in smoked, salted, and pickled foods as well as nitrates and nitrites; smoking; and obesity. Additional risk factors include previous stomach surgery; chronic atrophic gastritis; and hereditary syndromes, such as hereditary diffuse gastric cancer (associated with the diffuse type), Lynch syndrome, and familial adenomatous polyposis. Gastric intestinal metaplasia and dysplasia are also risk factors for gastric adenocarcinoma.

Screening and Surveillance

There is no recommendation for population-based screening for gastric adenocarcinoma in countries with a low incidence of gastric cancer, such as the United States. Intestinal metaplasia with high-grade dysplasia should be resected because 25% of cases progress to adenocarcinoma. Screening and surveillance are indicated for patients with familial adenomatous polyposis and Lynch syndrome.

Clinical Manifestations and Diagnosis

Symptoms of gastric adenocarcinoma may be vague. They include poor appetite, weight loss, abdominal pain, early satiety, nausea, and vomiting. Signs of gastric adenocarcinoma include iron deficiency anemia. Diagnosis is typically made by upper endoscopy with biopsy.

For treatment of gastric cancer, see MKSAP 19 Oncology.

KEY POINTS

- The primary nongenetic risk factor for gastric cancer is *Helicobacter pylori* infection.
- In countries with a low incidence of gastric cancer, such as the United States, screening for gastric cancer should be reserved for patients with genetic cancer syndromes. **HVC**
- Upper endoscopy with biopsy is the diagnostic test of choice for gastric cancer.

Gastric Surgery Complications

For complications of bariatric surgery, see MKSAP 19 General Internal Medicine 2.

Partial or complete gastric resections are performed for benign and malignant disease. The extent of resection, type of reconstruction, and nature of the disease affect postoperative morbidity and mortality. Partial resection allows preservation of some function of the stomach, but patients with malignancy require lifelong surveillance of the remaining stomach for recurrence. Patients who undergo partial gastrectomy for benign disease also have an increased risk for cancer in the gastric remnant 15 to 20 years after surgery, with reported frequency ranging from 0.8% to 8.9%.

Dumping syndrome, which results from rapid gastric emptying after gastric surgery, can cause significant postprandial gastrointestinal and vasomotor symptoms. Clinical features of early dumping syndrome occur within 30 minutes of eating due to gastrointestinal hormone hypersecretion, autonomic dysregulation, and bowel distention. Symptoms include palpitations, flushing or pallor, diaphoresis, light-headedness, hypotension, and fatigue, followed by diarrhea, nausea, abdominal bloating, cramping, and borborygmus. Symptoms of late dumping syndrome occur 1 to 3 hours after meals because of reactive hypoglycemia and can include decreased concentration, faintness, and altered consciousness. In severe cases, protein-wasting malnutrition can occur.

Roughly 25% to 50% of all patients who have undergone gastric surgery experience some symptoms of dumping syndrome, but severe, persistent symptoms occur in only about 10%. Oral glucose challenge testing helps make the diagnosis, with a sensitivity of nearly 100% and a specificity of 94%.

First-line treatment for dumping syndrome is dietary, with smaller, more frequent meals and ingestion of liquids after meals. Decreasing carbohydrate intake, especially simple carbohydrates, and increasing protein and fiber intake may also alleviate symptoms.

Acarbose, an α-glycosidase hydrolase inhibitor that interferes with digestion of polysaccharides to monosaccharides, can be used for late symptoms of dumping syndrome. Other pharmacologic therapies include anticholinergics to slow gastric emptying and antispasmodics. Severe cases of dumping rarely require octreotide. If a trial of subcutaneous injections is effective, monthly intramuscular injections of long-acting octreotide can be used.

KEY POINTS

- Patients who undergo partial gastrectomy for malignancy require lifelong surveillance for cancer recurrence; patients who have undergone partial gastrectomy for benign disease also have an increased risk for gastric cancer.
- Dumping syndrome results from rapid gastric emptying after gastric surgery; first-line treatment is smaller, more frequent meals with liquids taken following meals.

Disorders of the Pancreas

Acute Pancreatitis

Acute pancreatitis is an inflammatory process involving the pancreas and extrapancreatic organs and is the most common gastrointestinal cause of hospitalization in the United States. Biliary disease, including gallstones, biliary sludge, and biliary crystals (microlithiasis), is the most common cause of acute pancreatitis (**Table 14**). Premature activation of digestive enzymes and release of cytokines cause autodigestion of the pancreas and inflammation, which may involve surrounding tissues and distant organs.

Acute pancreatitis is classified as mild, moderately severe, or severe. Mild acute pancreatitis does not involve organ failure or other complications, usually resolves within 1 week, and has a low mortality rate. Twenty percent of patients with acute pancreatitis develop moderately severe or severe disease. Moderately severe acute pancreatitis involves local or systemic complications, such as necrosis or organ failure lasting less than 48 hours. Severe acute pancreatitis involves systemic inflammatory response syndrome (SIRS), persistent organ failure (usually kidney or respiratory failure), duration longer than 48 hours, and one or more local complications. The mortality rate is as high as 50%.

Clinical Presentation and Diagnosis

The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute-onset abdominal pain characteristic of pancreatitis (severe, persistent for hours to days, and epigastric in location, often radiating to the back); (2) serum lipase or amylase levels elevated at least three times the upper limit of normal; and (3) characteristic imaging findings (**Figure 9**). High fever and leukocytosis are part of the cytokine cascade and do not necessarily indicate infection.

TABLE 14. Causes of Acute Pancreatitis

Common
Biliary disease
Gallstones
Biliary sludge
Microlithiasis (1- to 2-mm stones that are not detected by imaging studies)
Alcohol use
Postendoscopic retrograde cholangiopancreatography
Occasional
Medications[a]
Furosemide
Didanosine
Asparaginase
Mesalamine
Thiazides
6-Mercaptopurine/azathioprine
Sulfasalazine
Simvastatin
Hypertriglyceridemia
Hypercalcemia
Type V choledochocele
Rare
Autoimmune
Infectious
Viral (mumps, coxsackie B virus, cytomegalovirus, hepatitis B virus, varicella-zoster virus, herpes simplex virus, HIV)
Parasitic (*Toxoplasma* species, *Ascaris lumbricoides*, *Cryptosporidium* species)
Bacterial (*Legionella*, *Leptospira*, *Mycoplasma*, and *Salmonella* species)
Fungal (*Aspergillus* species)
Ischemia
Trauma
Neoplasia
Celiac disease
Genetic (only if attacks recur)

[a] Multiple medications have been linked to acute pancreatitis. A partial list of other suspect medications includes metronidazole, pentamidine, stibogluconate, tetracycline, sulfasalazine, L-asparaginase, valproic acid, sulindac, salicylates, estrogen, and calcium.

Patients with acute pancreatitis should undergo transabdominal ultrasonography to assess for gallstones and biliary duct dilation. Transabdominal ultrasonography is preferred

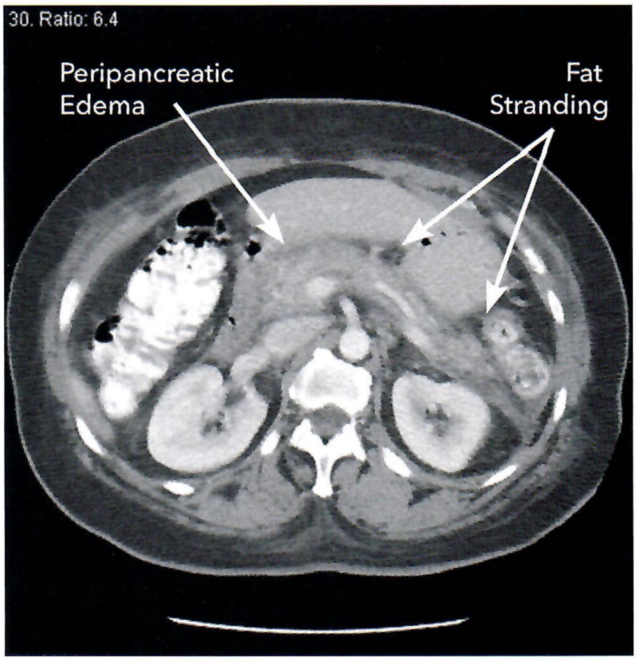

FIGURE 9. CT scan showing acute pancreatitis with peripancreatic fat stranding and inflammation. The hazy appearance of the mesenteric fat surrounding the pancreas in this image is called fat stranding, and the blurring of the margins of the pancreas is consistent with peripancreatic edema, features seen with inflammatory changes of acute pancreatitis.

over CT because it has a higher sensitivity for detecting gallstones, avoids the risks of intravenous contrast material, and is more cost-effective. Magnetic resonance cholangiopancreatography may be considered in patients without abnormal findings on ultrasonography when concern remains for concomitant biliary disease. Although less useful for assessing the biliary system, CT may be indicated if the diagnosis is in question or clinical symptoms are not improved within the first 48 hours (especially because abdominal air can limit ultrasonographic visualization of the pancreas).

A serum alanine aminotransferase level greater than 150 IU/L suggests gallstone pancreatitis. Hyperbilirubinemia should raise suspicion of biliary obstruction and/or cholangitis. Serum amylase and lipase levels may be elevated in conditions other than acute pancreatitis, such as kidney disease, acute appendicitis, cholecystitis, intestinal obstruction or ischemia, peptic ulcer, or gynecologic disorders. Enzyme levels may be falsely low or normal in patients with hypertriglyceridemia-induced pancreatitis because of lipemic-serum interference with laboratory assays. Triglyceride levels should be measured in patients without a biliary cause of acute pancreatitis; a triglyceride level exceeding 1000 mg/dL (11.3 mmol/L) can be considered the cause of the acute pancreatitis.

Prognostic Criteria

Risk factors for severe disease include age older than 55 years, medical comorbidities, BMI greater than 30, presence of SIRS, signs of hypovolemia on presentation (e.g., serum blood urea nitrogen level >20 mg/dL [7.1 mmol/L] and rising, hematocrit >44%, or elevated serum creatinine level), presence of pleural effusions and/or infiltrates, and altered mental status. A systematic review of 18 multiple-factor scoring systems, including the Ranson criteria and the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, for predicting outcome in acute pancreatitis found these systems to have limited clinical value and accuracy. Scoring systems identify severe disease only as it develops, without enough lead time for intervention, and they are too cumbersome for routine use. Elevated hematocrit, elevated blood urea nitrogen levels, and the presence of SIRS are as accurate as complex scoring systems in predicting outcome, and they are easier to use.

Management

Mainstays of initial management include fluid resuscitation, pain management, and antiemetics.

Early and aggressive fluid resuscitation (250-500 mL/h of intravenous normal saline or lactated Ringer solution) should be given to patients with acute pancreatitis on presentation and is most beneficial in the first 12 to 24 hours. More rapid fluid resuscitation (boluses) may be needed in patients with severe volume depletion in order to maintain organ perfusion. Patients with organ failure or SIRS should be admitted to an ICU or intermediary care setting, with fluid requirements reassessed every 6 hours for the first 24 to 48 hours.

Routine use of antibiotics is not warranted in acute pancreatitis unless there is evidence of extrapancreatic infection, such as ascending cholangitis, bacteremia, urinary tract infection, or pneumonia. Use of prophylactic antibiotics in patients with sterile pancreatic necrosis to prevent infected necrosis is not recommended.

In mild acute pancreatitis, oral feedings can be started as soon as nausea and vomiting are controlled and clinical symptoms improve. Enteral feeding should begin within 72 hours if oral feeding is not tolerated; it is usually required in patients with moderately severe or severe acute pancreatitis. Feeding with a nasojejunal tube has traditionally been preferred, but data suggest that nasogastric feedings are probably as effective and are easier to administer. Enteral feeding promotes a healthy gut-mucosal barrier and may prevent translocation of bacteria into inflamed tissues.

If a biliary cause of acute pancreatitis is suspected, serial liver chemistry tests and clinical symptoms can show whether the biliary obstruction is ongoing or resolving. Endoscopic retrograde cholangiopancreatography (ERCP) is not indicated in patients with gallstone pancreatitis unless there is persistent biochemical evidence of biliary obstruction or choledocholithiasis is seen on imaging. Patients with cholangitis should undergo ERCP within 24 hours of admission. Magnetic resonance cholangiopancreatography can be useful when there is persistent elevation of liver chemistries without overt cholangitis or biliary obstruction. Patients with uncomplicated gallstone pancreatitis should be considered for cholecystectomy before discharge.

There is no value in rechecking serum amylase and lipase levels after the diagnosis is established.

Complications

There are two overlapping phases of acute pancreatitis with two peaks in mortality. The early phase is the first week of the disease. In this phase, the body is responding to local pancreatic injury and the cytokine cascade; SIRS and organ failure, especially kidney and respiratory failure, are possible, as is profound hypocalcemia. The late phase occurs after the first week and may persist for weeks to months in patients with moderately severe or severe acute pancreatitis. Significant risk for infection in peripancreatic fluid collections and necrotic tissue occurs in the late phase.

Proper classification of fluid collections in acute pancreatitis is important to guide management. In 2012, an international consensus group updated the Atlanta classification and definitions of acute pancreatitis and its complications to promote consistency in diagnosis and management. The group defined four types of fluid collections:

1. Acute peripancreatic fluid collections occur in edematous interstitial pancreatitis (no necrosis) within the first 4 weeks, are thought to result from rupture of main or side-branch ducts because of inflammation, are sterile, and usually resolve spontaneously.
2. Pancreatic pseudocysts are acute peripancreatic fluid collections that have persisted for longer than 4 weeks, have developed a well-defined wall, and contain no solid debris (necrosis).
3. Acute necrotic collections (**Figure 10**) are areas of necrosis in the pancreatic parenchyma and/or peripancreatic tissues within the first 4 weeks of acute pancreatitis.

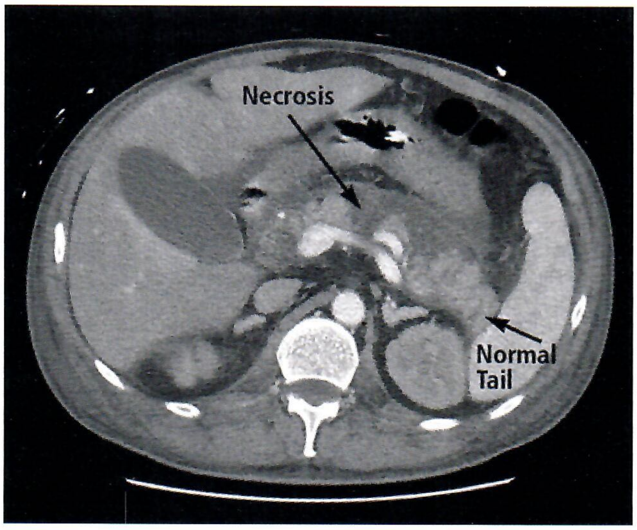

FIGURE 10. CT scan showing acute pancreatitis with hypoperfusion of the body of the pancreas, as indicated by lack of enhancement following intravenous contrast infusion (necrosis) and normal perfusion of the pancreatic tail.

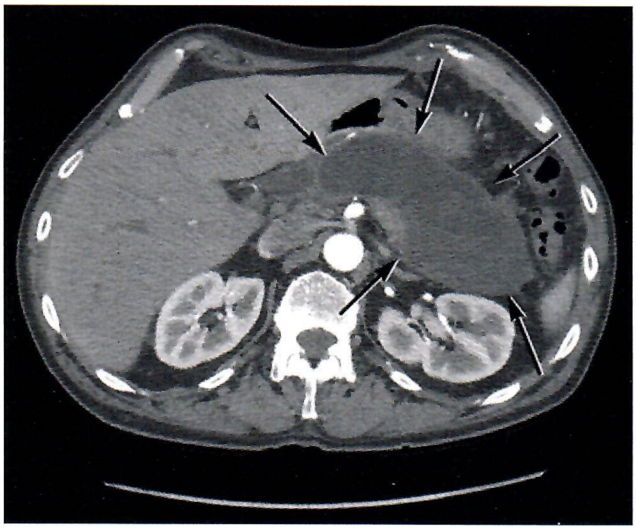

FIGURE 11. CT scan showing maturation and liquefaction of pancreas necrosis of nearly the entire pancreas over 4 weeks' duration with a well-defined rim or wall (*arrows*), known as walled-off necrosis.

4. Walled-off necrosis (**Figure 11**) occurs after 4 weeks, when the body liquefies the necrosis and contains it within a well-defined wall.

Contrast-enhanced CT may not be able to distinguish solid from liquid content in fluid collections; therefore, necrotic collections are frequently misdiagnosed as pancreatic pseudocysts. Pancreatic pseudocysts do not require drainage unless they cause significant symptoms or are infected, regardless of size.

Because they contain only fluid, pseudocysts are easily drained under endoscopic or radiographic guidance. Walled-off necrosis is not as amenable to percutaneous or endoscopic drainage because of solid necrotic debris within the cavity and may require surgical debridement.

The management of suspected infected necrosis includes initiation of antibiotics (e.g., imipenem-cilastatin, meropenem, or ciprofloxacin plus metronidazole), with consideration of fine-needle aspiration with Gram stain and culture under CT guidance. Drainage procedures or debridement should be delayed for at least 4 weeks if possible to allow encapsulation of the necrosis with a fibrous wall.

KEY POINTS

- Biliary disease (gallstones, biliary sludge, or microlithiasis) is the most common cause of acute pancreatitis.
- Diagnosis of acute pancreatitis requires two of three criteria: (1) acute-onset upper abdominal pain, (2) serum lipase or amylase levels elevated at least three times the upper limit of normal, and (3) characteristic findings on imaging.
- Patients with acute pancreatitis should undergo transabdominal ultrasonography rather than CT for evaluation of biliary disease. **HVC**

(Continued)

KEY POINTS ***(continued)***

- Early and aggressive fluid resuscitation should be initiated in patients with acute pancreatitis.
- In mild acute pancreatitis, oral feedings can be started as soon as nausea and vomiting are controlled and clinical symptoms are alleviated; enteral feeding should begin within 72 hours if oral feeding is not tolerated.
- Pancreatic pseudocysts do not require drainage unless they cause significant symptoms or are infected, regardless of size.

Chronic Pancreatitis

Chronic pancreatitis is thought to develop when the inflammatory response to acute pancreatitis persists and ongoing inflammation activates stellate cells, resulting in a fibroinflammatory response. This causes distorted tissue architecture, loss of normal parenchyma, activation of pancreatic nociceptors, and loss of acinar and islet cell function. Genetic variants affecting inflammatory response, enzyme activation, and tissue repair are thought to play important roles in the pathogenesis of chronic pancreatitis. Many genes have been identified as disease modifiers, but the gene-environment interaction is not fully understood.

Alcohol use has long been described as a risk factor for chronic pancreatitis, but less than 3% of heavy alcohol users develop pancreatic disease. Patients who consume more than five drinks per day (or 35 drinks per week) seem to be more susceptible to chronic pancreatitis. In the largest study of patients with chronic pancreatitis in North America, only 46% had a history of significant alcohol use. The higher prevalence of alcohol-associated pancreatitis among men could be partially explained by an X chromosome–linked genetic variant, the *CLDN2* gene. Tobacco is considered an independent risk factor. **Table 15** lists causes of chronic pancreatitis.

TABLE 15. Causes of Chronic Pancreatitis
Toxic or metabolic
Alcohol, tobacco, hypercalcemia, hypertriglyceridemia, chronic kidney disease
Genetic
Mutations or polymorphisms of the *CFTR*, *PRSSI*, *SPINKI*, *CTRC*, *CASR*, *CLDN2* genes
Recurrent and severe acute pancreatitis
Vascular disease/ischemia
Obstructive
Pancreatic tumor, intraductal papillary mucinous neoplasm
Posttraumatic (pancreatic duct stricture)
Autoimmune (type 1 and type 2)
Idiopathic

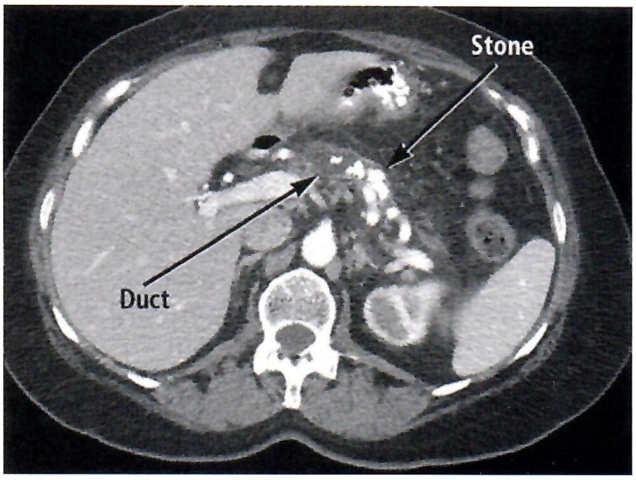

FIGURE 12. CT scan showing chronic calcific pancreatitis with multiple stones in the main duct and side branches of the pancreas.

Clinical Presentation and Diagnosis

Abdominal pain is the most common presenting symptom of chronic pancreatitis (seen in 85% of patients), but some patients have no pain. Pain patterns can vary from constant daily pain to intermittent attacks of severe pain. Pancreatic enzyme levels may not increase during attacks of pain because of fibrosis and atrophy of acinar cells and decreased enzyme production. Constant daily pain in chronic pancreatitis significantly reduces quality of life, with increased use of health care resources and disability benefits and time away from employment. Exocrine or endocrine insufficiency occurs in some patients as a result of significant tissue destruction.

Diagnosis of chronic pancreatitis remains challenging because hallmark anatomic features, such as pancreatic calcifications (**Figure 12**), occur in only 25% of patients, and other features of atrophy or duct dilation can occur normally with aging or other disease processes. Imaging with CT or MRI is the initial test of choice. In the setting of high clinical suspicion and negative findings on imaging, endoscopic ultrasonography and secretin-enhanced magnetic resonance cholangiopancreatography may be useful as second- and third-line tests; pancreatic biopsy may rarely be necessary. ERCP is no longer used as a diagnostic tool for chronic pancreatitis. Genetic testing for cystic fibrosis and familial pancreatitis should be considered in younger patients. Pancreatic exocrine function may be assessed with fecal elastase testing, which has largely replaced fecal fat testing.

Management

Management focuses on treating symptoms. No effective treatment exists to reverse or halt disease progression. Patients should be counseled to avoid alcohol and tobacco to lessen attacks of inflammation and pain. Intermittent attacks of severe acute pain are treated as acute pancreatitis. Possible complications of chronic pancreatitis, including pseudocyst, pancreatic duct stones causing upstream obstruction, and malignancy, should be evaluated with imaging (e.g., pancreatic-protocol CT) when a patient's symptom pattern changes. Endoscopic techniques are first-line therapy for relief of ductal obstruction. Constant daily pain is more challenging to manage; treatment frequently involves medications such as tramadol, serotonin norepinephrine reuptake inhibitors, gabapentinoids, and opioids. Long-term use of opioids should be avoided because of hyperesthesia and development of tolerance or addiction. Pancreatic enzymes are used to treat steatorrhea but do not effectively treat pain or prevent attacks of pancreatitis. Two large randomized trials of antioxidants to treat chronic pancreatitis pain showed conflicting results; guidelines suggest that antioxidants be considered, although it is unclear which antioxidants and doses are appropriate. Nerve blocks and neurolysis procedures are also recommended, although the response rate is low, and pain relief, if achieved, lasts only a few weeks.

Surgery offers the best long-term results for chronic refractory pain management and, depending on anatomy and cause, may include lateral pancreaticojejunostomy, duodenal-preserving pancreatic head resection, pancreaticoduodenectomy, distal pancreatectomy, or even total pancreatectomy with or without auto-islet-cell transplantation. These procedures improve outcomes in patients at high-volume pancreas referral centers. Pancreatic endocrine insufficiency may require specialty referral for labile diabetes management.

KEY POINTS

- Abdominal pain, which may occur as intermittent attacks or as ongoing daily pain, is the most common symptom of chronic pancreatitis.
- **HVC** Pancreatic biopsy and endoscopic retrograde cholangiopancreatography are not indicated in the diagnosis of chronic pancreatitis.
- Symptomatic management is the cornerstone of treatment for chronic pancreatitis, including in patients with refractory pain.
- Patients with chronic pancreatitis should be counseled to avoid alcohol and tobacco use.

Autoimmune Pancreatitis and IgG4 Disease

Autoimmune pancreatitis (AIP) is a frequent manifestation of IgG4-related disease. Other organs that can be affected include the lacrimal and salivary glands, central nervous system, kidneys, thyroid gland, lungs, biliary tract and liver, prostate gland, retroperitoneum, and lymph nodes. Storiform fibrosis and obliterative phlebitis are seen in the pancreas and biliary tract. The most common pancreatic manifestation of IgG4-related disease is type 1 AIP, with abundant infiltration of IgG4-positive plasma cells and lymphocytes. Type 2 disease is discussed in Clinical Presentation and Diagnosis. The 2011 International Consensus of Diagnostic Criteria for Autoimmune Pancreatitis endorsed the concept of type 1 and type 2 disease, but there is some debate over whether type 2 should be considered an IgG4-related disease.

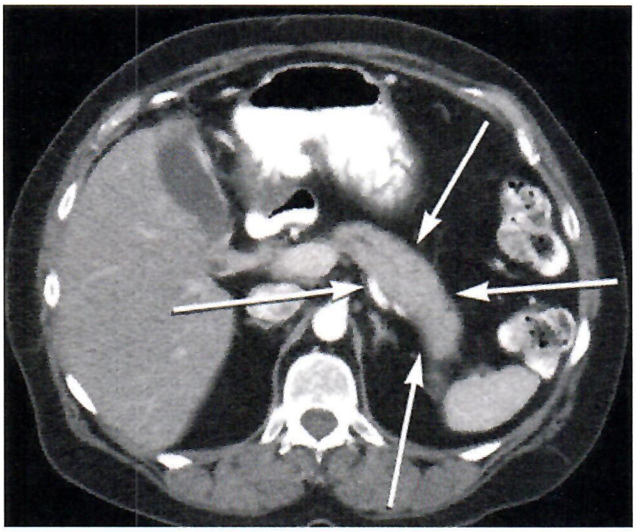

FIGURE 13. CT scan showing the homogeneous, hypodense "sausage-shaped" swelling (*arrows*) seen in autoimmune pancreatitis. The pancreatic duct is not dilated.

For more information on IgG4-related disease, see MKSAP 19 Rheumatology.

Clinical Presentation and Diagnosis

Patients with both types of AIP may present with abdominal pain or obstructive jaundice with or without a mass. In patients presenting with obstructive jaundice or with a mass, pancreatic malignancy must be considered. Many patients with malignancy have a dilated upstream main pancreatic duct. In contrast, patients with AIP may have a narrowed main pancreatic duct or parenchymal swelling ("sausage-shaped" pancreas [**Figure 13**]). Endoscopic ultrasonography and biopsy may be required to differentiate AIP and pancreatic neoplasm. Ten percent of patients with type 1 AIP may develop chronic pancreatitis or pancreatic stone formation.

Patients with type 1 AIP have elevated levels of IgG4-positive cells in pancreatic tissue (>10 IgG4-positive cells/hpf), and 60% to 80% of patients have associated sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Fulfillment of one or more of the HISORt criteria (diagnostic Histology, suggestive Imaging, Serology with elevated serum IgG4, Other organ involvement, or Response to therapy with glucocorticoids) can be helpful in the diagnosis of type 1 AIP.

Type 2 AIP has no or few IgG4-positive cells but is characterized by idiopathic duct-centric neutrophil infiltration, known as a granulocytic epithelial lesion. Type 2 AIP is a pancreas-specific disease occasionally associated with inflammatory bowel disease.

Treatment

Glucocorticoids are effective treatment for types 1 and 2 AIP, starting with oral prednisolone at 0.6 to 1.0 mg/kg/d and tapered over 2 to 3 months. Response is determined by symptom relief and imaging features. Failure of clinical symptoms to respond to glucocorticoids suggests an incorrect diagnosis, and other causes should be investigated. Up to 60% of patients may relapse. Glucocorticoids or immunomodulators, such as 6-mercaptopurine, azathioprine, mycophenolate, or rituximab, may be re-adminstered to treat recurrent AIP.

KEY POINTS

- Diagnosis of autoimmune pancreatitis requires the presence of a narrowed main pancreatic duct and parenchymal swelling ("sausage-shaped" pancreas) on imaging and disease response to glucocorticoids.
- Type 1 autoimmune pancreatitis is characterized by elevated numbers of IgG4-positive cells in pancreatic tissue; most patients also have a significant elevation of IgG4 in serum.
- Patients with type 2 autoimmune pancreatitis have normal IgG4-positive cell counts.
- Types 1 and 2 autoimmune pancreatitis are treated with glucocorticoids, with a relapse rate of up to 60%.

Pancreatic Adenocarcinoma

Pancreatic ductal adenocarcinoma has a poor prognosis and increasing incidence. In 2019, there were approximately 57,000 cases diagnosed in the United States and 46,000 deaths. It is predicted to become the second leading cause of cancer-related death in the United States over the next decade, with an overall 5-year survival rate of 9%.

Epidemiology and Risk Factors

Risk factors for pancreatic cancer include age older than 50 years, smoking history, obesity, chronic pancreatitis, and mucinous cystic lesions of the pancreas. Inherited conditions associated with pancreatic cancer include Peutz-Jeghers syndrome, *BRCA2* germline mutations, hereditary pancreatitis, familial atypical multiple-mole melanoma, Lynch syndrome, and familial pancreatic cancer with at least two affected first-degree relatives.

Clinicians should not screen average-risk individuals for pancreatic cancer. The American Gastroenterological Association and the International Cancer of the Pancreas Screening Consortium recommend that clinicians screen select high-risk patients for pancreatic cancer, including those with a genetic predisposition to disease. If possible, screening should be performed at a center experienced in the diagnosis and treatment of pancreatic adenocarcinoma.

Clinical Presentation

Symptoms of pancreatic adenocarcinoma include abdominal pain, back pain, weight loss, and jaundice (if the lesion obstructs the common bile duct). Pancreatic cancer is highly associated with diabetes mellitus, and two thirds of patients develop new-onset diabetes mellitus in the 36 months surrounding the diagnosis. Venous thromboembolic events and depression occur at higher rates in patients with pancreatic adenocarcinoma than in patients with other malignancies.

Diagnosis

Pancreas-protocol CT uses multiphasic arterial and venous phases with thin cuts (3 mm) through the abdomen to view the primary tumor's relationship to mesenteric vasculature and to detect metastatic lesions. Some studies suggest that pancreas-protocol MRI may be superior to CT for pancreatic disease. Histopathologic confirmation of pancreatic adenocarcinoma is increasingly recommended before initiation of therapy. In patients with potentially resectable disease, endoscopic ultrasonography–guided fine-needle aspiration biopsy is recommended for histologic confirmation of cancer. It is preferable to CT-guided biopsy because of its higher diagnostic yield, safety, and lower risk for peritoneal seeding. Patients are considered for primary surgical resection if they have no involvement of mesenteric vasculature or metastatic disease and are healthy enough for major intra-abdominal surgery.

For staging and treatment of pancreatic cancer, see MKSAP 19 Oncology.

KEY POINTS

- Diagnosis of pancreatic cancer is suggested by abdominal pain, weight loss, jaundice, and new-onset diabetes mellitus; pancreas-protocol CT or MRI helps support the diagnosis and delineates the extent of disease.
- In patients with potentially resectable disease, endoscopic ultrasonography–guided fine-needle aspiration of the pancreas is recommended for histologic confirmation of cancer.

Cystic Lesions of the Pancreas

Pancreatic cysts are found incidentally in 15% of patients undergoing abdominal imaging. The detection of a cystic lesion in the pancreas causes anxiety in patients and clinicians and is a growing driver of health care use in the United States.

Cystic neoplasms of the pancreas are subcategorized as mucin-producing and nonmucin-producing cysts (**Figure 14**). Mucin-producing cysts, including intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, are thought to have malignant potential, but many never become malignant. Intraductal papillary mucinous neoplasms are the most common cystic lesions of the pancreas. Most intraductal papillary mucinous neoplasms arise from a side branch of the pancreatic duct and have a low rate of malignant transformation. In contrast, the rate of malignant transformation is as high as 65% in intraductal papillary mucinous neoplasms involving the main pancreatic duct (**Figure 15**). Other worrisome features are presence of symptoms (jaundice, pancreatitis), cyst size greater than 3 cm, dilated main pancreatic duct, and a solid cyst component.

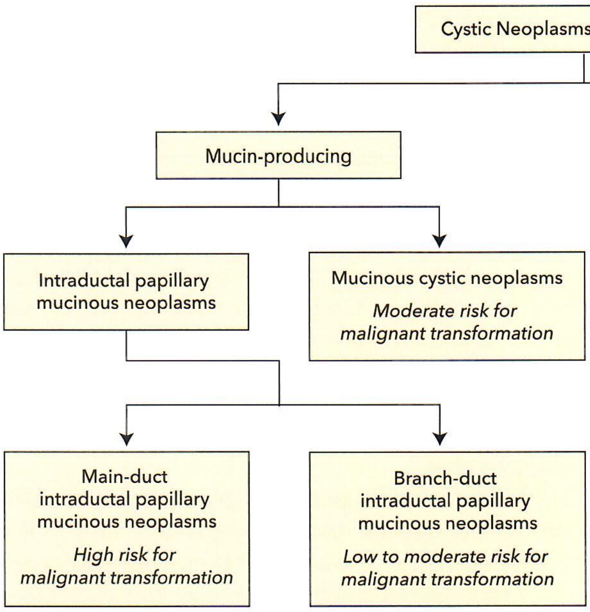
Cystic Neoplasms of the Pancreas
Mucin-producing
Non-mucin-producing
Intraductal papillary mucinous neoplasms
Mucinous cystic neoplasms
Moderate risk for malignant transformation
Serous cystic tumors
Minimal risk for malignant transformation
Solid pseudopapillary neoplasms
Moderate to high risk for malignant transformation
Main-duct intraductal papillary mucinous neoplasms
High risk for malignant transformation
Branch-duct intraductal papillary mucinous neoplasms
Low to moderate risk for malignant transformation

FIGURE 14. Types and malignant potential of cystic neoplasms of the pancreas.

Non-mucin-producing cysts, such as a serous cystadenoma, have no malignant potential and can often be identified by their characteristic imaging features. These cysts require no further evaluation unless symptomatic.

Mucinous cystic neoplasms are seen almost exclusively in women (more than 98%) and found in the pancreas body or tail in 90% of cases; they have a higher malignant potential than intraductal papillary mucinous neoplasm. A thick fibrous capsule with epithelioid cells (similar to ovarian stroma) surrounds the tumor. Differentiating mucinous cysts from serous cysts, pseudocysts, and cystic neuroendocrine tumors of the pancreas can be challenging because there is no definitive test with high sensitivity and specificity. Endoscopic ultrasonography with fine-needle aspiration is used for cyst fluid analysis in worrisome lesions; cyst fluid carcinoembryonic antigen levels are frequently elevated in patients with mucinous cysts, whereas cyst amylase levels are often elevated in patients with pseudocysts. Cytology of cyst fluid has a low sensitivity (<60%) and is an unreliable predictor of malignant transformation.

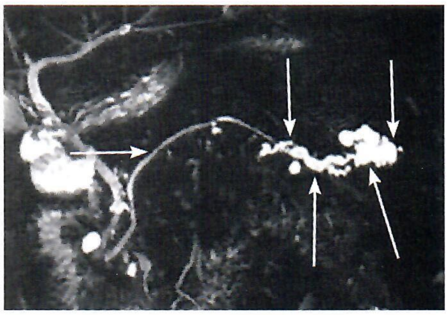

FIGURE 15. Magnetic resonance cholangiopancreatogram of a main-duct intraductal papillary mucinous neoplasm of the tail of the pancreas. Cystic dilation of the main pancreatic duct in the tail is seen (*arrows*).

Surgical resection of high-risk cysts, including intraductal papillary mucinous neoplasms involving the main duct, is the only treatment option. Multiple guidelines on surveillance of pancreatic cystic neoplasms have been published, with differing recommendations based on target populations, clinical variables (symptomatic or asymptomatic), and initial and long-term surveillance recommendations.

KEY POINTS

- Most pancreatic cysts never become malignant; intraductal papillary mucinous neoplasms involving the main pancreatic duct have the highest risk for malignant transformation.
- High-risk cysts are managed with surgical resection.

Other Pancreatic Tumors

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (NETs) are rare, representing 3% of primary pancreatic neoplasms. About 10% to 25% of pancreatic NETs are functional and hypersecrete hormones. Nonfunctional NETs are often discovered incidentally. The liver is the most common site of metastases. Most functional pancreatic NETs secrete gastrin (gastrinoma) or insulin (insulinoma). Glucagon, vasoactive intestinal peptide, adrenocorticotropic hormone, somatostatin, serotonin, and parathyroid hormone-related hormone levels may be measured as clinically indicated. Genetic testing for multiple endocrine neoplasia type 1 is recommended in all young patients with gastrinomas or insulinomas and in any patient with a family or personal history of other endocrinopathies or multiple pancreatic NETs. Pancreatic NETs may be sporadic or due to hereditary tumor syndromes, and genetic testing should be considered in these cases.

Imaging is recommended with multiphasic CT or MRI of the abdomen. Endoscopic ultrasonography (90% sensitive), octreotide scintigraphy, or somatostatin-based PET may be needed to detect small lesions. For functional pancreatic NETs, surgery is recommended if more than 90% of the tumor can be resected. For nonfunctional tumors associated with multiple endocrine neoplasia type 1 and von Hippel-Lindau syndrome, surgery is usually recommended if the tumors exceed 2 to 3 cm. Medical management of gastrinomas includes oral proton pump inhibitors two or three times daily or somatostatin analogs. High-volume or progressive disease is best managed in conjunction with a gastroenterologist. See MKSAP 19 Oncology for further information on staging and treatment.

Ampullary Adenocarcinoma

Adenocarcinoma of the ampulla of Vater accounts for 0.2% of gastrointestinal malignancies and usually presents early because of obstruction of the biliary system. Endoscopic ultrasonography with biopsy is the preferred method for staging and tissue diagnosis, with 90% accuracy. At least 50% of patients with familial adenomatous polyposis syndrome develop adenomatous changes of the periampullary region, which may progress to adenocarcinoma. See Colorectal Neoplasia for more information on adenomatous polyposis syndromes. Hereditary tumor syndromes can cause ampullary adenocarcinomas; patients should be considered for genetic testing.

KEY POINT

- About 10% to 25% of pancreatic neuroendocrine tumors are functional and hypersecrete hormones, most commonly gastrin or insulin.

Disorders of the Small and Large Bowel

Diarrhea

Classification

Diarrhea is marked by passage of a greater number of less-formed stools than normal. Diarrhea is considered acute if occurring for fewer than 2 weeks and chronic if occurring for at least 4 weeks. Acute diarrhea is usually infectious, whereas chronic diarrhea is usually noninfectious.

Acute Diarrhea

Causes

Causes of acute diarrhea include bacteria, viruses, and parasites. These can be divided into noninvasive and invasive causes. Noninvasive causes, leading to watery diarrhea, include *Clostridioides difficile*, viruses (e.g., norovirus), *Escherichia coli*, cholera, cryptosporidia, and *Giardia duodenalis*. Invasive causes lead to dysentery or bloody diarrhea and include *Campylobacter*, hemorrhagic *E. coli*, *Entamoeba histolytica*, *Shigella*, and *Salmonella*. Persistent diarrhea (14-30 days) is usually caused by a parasite. See MKSAP 19 Infectious Disease for further discussion of infectious diarrhea.

Evaluation

Acute diarrhea may be accompanied by abdominal cramping, tenesmus, flatulence, fever, nausea, and vomiting. For patients with acute diarrhea, evaluation of hydration status is important. Stool testing for infectious causes depends on suspicion of disease outbreak, symptom severity, symptom duration (>7 days), and increased risk for infectious diarrhea (e.g., worker in health care or food preparation).

Management

Fluid therapy is the mainstay of treatment for acute diarrhea. Patients with severe diarrhea or travelers with cholera-like diarrhea should receive balanced electrolyte rehydration solutions. Hospitalization is usually unnecessary except for severe disease, hemodynamic instability, or multiple medical comorbidities. Confirmed *C. difficile* infection should be treated according to comorbidities and clinical severity (see MKSAP 19 Infectious Disease for discussion of *C. difficile* infection). Treatment of diarrhea in travelers includes bismuth and loperamide to relieve symptoms and possibly empiric antibiotics for moderate or severe symptoms.

Chronic Diarrhea

Causes

Chronic diarrhea can be grouped into six categories by disease mechanism: (1) osmotic, (2) secretory, (3) steatorrhea, (4) inflammatory, (5) motility, and (6) miscellaneous (**Table 16**). These categories may overlap because some diseases have multiple mechanisms causing diarrhea. The most common causes are irritable bowel syndrome with predominant diarrhea (IBS-D) and functional causes. Medications are also an important cause (**Table 17**).

Evaluation

Evaluation of chronic diarrhea includes a careful history and physical examination. Because IBS-D and functional causes are the most common, further diagnostic studies should be reserved for patients whose symptoms or examination findings suggest another cause.

History and Physical Examination

The diarrhea pattern and stool characteristics can help determine the most likely diagnosis. Steatorrhea is often described as malodorous, greasy, or oily stools that float. The relation of symptoms to eating can also provide clues to the cause. Osmotic diarrhea occurs with eating and subsides with fasting, whereas secretory diarrhea does not subside with fasting. Nocturnal symptoms are often related to inflammatory conditions, such as inflammatory bowel disease (IBD). Information about specific dietary factors that commonly cause osmotic

TABLE 16. Types of Chronic Diarrhea

Diarrhea Type	Causes (examples)
Osmotic	Medications (laxatives)
	Undigested sugars (lactose, fructose, sorbitol, mannitol)
Secretory	Medications (nonosmotic laxatives, antibiotics)
	Endocrine (neuroendocrine tumors, adrenal insufficiency, hyperthyroidism)
	Bile salt malabsorption (ileal resection, cholecystectomy)
	Noninvasive infections (giardiasis, cryptosporidiosis)
	Small intestinal bacterial overgrowth
Steatorrhea	Maldigestion (decreased bile salts, pancreatic dysfunction)
	Malabsorption (celiac disease, tropical sprue, giardiasis, Whipple disease, chronic mesenteric ischemia, short bowel syndrome, small intestinal bacterial overgrowth, lymphatic obstruction)
Inflammatory	Inflammatory bowel disease (ulcerative colitis, Crohn disease, microscopic colitis)
	Malignancy (colorectal cancer, lymphoma)
	Invasive infections (*Clostridioides difficile*, cytomegalovirus, *Entamoeba histolytica*, tuberculosis)
	Ischemia
	Radiation colitis/enteritis
Motility	Postsurgical (vagotomy, dumping)
	Endocrine (diabetes mellitus, hyperthyroidism)
	Systemic sclerosis
Miscellaneous	Irritable bowel syndrome
	Functional diarrhea[a]
	Factitious
	Overflow
	Fecal incontinence

[a] Frequent or loose or watery stools without abdominal discomfort in the absence of other identifiable causes.

Adapted with permission from Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392. © 2013 Journal of Gastroenterology and Hepatology Foundation and Wiley Publishing Asia Pty Ltd.

diarrhea, such as lactose, fructose, or artificial sweeteners (sorbitol), should be obtained. The patient should be asked about new medications (prescription and nonprescription) and timing of the initiation of medication in relation to diarrhea onset. Concomitant symptoms may also suggest a diagnosis. Abdominal pain accompanying diarrhea may suggest IBS-D, especially when a bowel movement relieves pain. Rectal bleeding and weight loss suggest malignancy in older patients or IBD in younger patients.

TABLE 17. Medications That Cause Diarrhea

Common
Antacids, proton pump inhibitors
Chemotherapy
Antibiotics
Colchicine
Metformin
NSAIDs, mesalamine
Cholesterol-lowering drugs
Rarer
ACE inhibitors
Angiotensin receptor blockers
β-adrenergic receptor antagonists
Carbamazepine
Lipase inhibitors
Lithium
Prostaglandin
Vitamin/mineral supplements

Adapted with permission from Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392. © 2013 Journal of Gastroenterology and Hepatology Foundation and Wiley Publishing Asia Pty Ltd.

Epidemiologic factors may also be helpful. Conditions such as IBS and microscopic colitis are more common in women than men. IBS onset is most common in the third and fourth decades of life, microscopic colitis is most common in the seventh and eighth decades, and malignancy is suggested by onset at age 50 years and older.

Physical examination should assess for hydration and nutrition status, perineal disease suggesting Crohn disease, and sphincter defects suggesting fecal incontinence.

Additional Testing

The decision to pursue additional testing, including serologies, stool studies, imaging, and endoscopy, depends on the clinical scenario and likelihood of specific diseases. Complete blood count, iron studies (including ferritin), thyroid-stimulating hormone level, and testing for celiac disease and *C. difficile* infection may be considered.

For chronic diarrhea without an underlying diagnosis, stool studies can help clarify the cause. Analysis of stool includes fecal weight, stool electrolytes, fecal pH, fat content, fecal calprotectin, and presence of blood and leukocytes. In watery stools, fecal electrolytes can be used to calculate the fecal osmotic gap:

$$290 - (2 \times [\text{stool sodium} + \text{stool potassium}])$$

An osmotic gap less than 50 mOsm/kg (50 mmol/kg) suggests secretory diarrhea, and a gap exceeding 100 mOsm/kg (100 mmol/kg) suggests osmotic diarrhea.

Blood or leukocytes in the stool or an elevated fecal calprotectin level suggests an inflammatory cause. A positive 72-hour stool collection for fecal fat confirms steatorrhea; a random fecal fat assessment may be helpful if timed collection is not possible. A reduced fecal elastase level is useful for evaluating exocrine pancreatic function. When laxative abuse is suspected, a stool or urine laxative screen can aid in diagnosis.

For suspected small-bowel disease, small intestine evaluation may include small-bowel radiography, CT, or magnetic resonance enterography to identify conditions that could lead to bacterial overgrowth, such as small intestinal diverticular disease, inflammation, or strictures. Upper endoscopy is indicated when small-bowel mucosal disease (e.g., celiac disease or chronic infection) is suspected. Capsule endoscopy can visualize the small intestine but does not allow sampling. Device-assisted enteroscopy can be used in selected patients who require sampling of small intestinal tissue based on abnormalities found on imaging or capsule endoscopy. Diagnostic yields for capsule endoscopy and device-assisted enteroscopy are low in patients with chronic diarrhea and normal laboratory or imaging results.

Colonoscopy is the primary diagnostic tool for evaluating colonic causes of diarrhea, such as IBD, microscopic colitis, chronic colon infections, and malignancy. Colon biopsies of the right and left colon are required to exclude microscopic colitis. Colonoscopy is especially important in patients with rectal bleeding and/or age older than 50 years.

Additional testing (including HIV testing) may be warranted in immunocompromised patients and patients with secretory diarrhea. Patients found to have a small-bowel tumor in the setting of diarrhea should be considered for additional testing, including radioimmunoassays for peptides and/or 24-hour urine 5-hydroxyindoleacetic acid measurement for neuroendocrine tumors. Testing for gastrointestinal neuroendocrine tumors should be limited to patients with chronic diarrhea and flushing.

Management

Treatment of IBS-D is discussed in the Irritable Bowel Syndrome section. Treatment of osmotic diarrhea includes following a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) (**Table 18**) and lactose-free diet.

TABLE 18. Sources of FODMAP Carbohydrates

Fructose: honey, apples, pears, peaches, mangos, fruit juice, dried fruit
Lactose: milk, custard, ice cream, yogurt, soft cheeses
Fructans: wheat, rye, onions, leeks, zucchini
Galactans: legumes
Sugar alcohols: xylitol, sorbitol, maltitol, mannitol

FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Treatment of secretory diarrhea is aimed at identifying the cause and careful management of hydration. Repletion of fat-soluble vitamins is important in cases of fat malabsorption.

Medication-induced diarrhea necessitates changing medications unless the benefits exceed the potential harms and the patient considers the diarrhea manageable.

KEY POINTS

- Acute diarrhea (less than 2 weeks' duration) is usually caused by infectious agents; chronic diarrhea (more than 4 weeks' duration) is most commonly noninfectious.
- Maintaining hydration is the primary goal of treatment for acute diarrhea.
- The primary causes of chronic diarrhea are irritable bowel syndrome with predominant diarrhea, functional causes, and medications.

Microscopic Colitis

Microscopic colitis is characterized by normal mucosal appearance on endoscopy, with inflammatory changes seen on histopathology of colon biopsy specimens. Subclassification into lymphocytic colitis and collagenous colitis (**Figure 16**) is based on predominating histologic features. It mostly affects middle-aged and older women and is associated with other autoimmune conditions, particularly celiac disease. It presents with abrupt or gradual onset of watery diarrhea that has a relapsing-remitting course over months to years, sometimes accompanied by mild weight loss and abdominal pain.

Several medication classes, including NSAIDs, selective serotonin reuptake inhibitors, and proton pump inhibitors, are associated with microscopic colitis. The first step in management is discontinuing potentially causative medications and symptomatic treatment with antidiarrheal agents, such as loperamide. First-line treatment is budesonide. Second-line treatments include bismuth subsalicylate, prednisone, or mesalamine and are considered when patient preference, side effects, or cost make budesonide impractical. Patients with

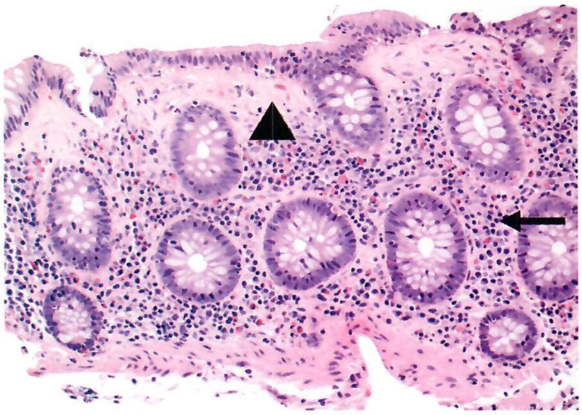

FIGURE 16. Collagenous colitis: colon mucosal biopsy specimen showing a pink, abnormal subepithelial collagen band (*arrowhead*) and lamina propria expanded by inflammatory cells (*arrow*).

microscopic colitis have no long-term increased risk for colorectal cancer.

Celiac Disease and Nonceliac Gluten Sensitivity

Celiac disease is an immune-mediated disease that primarily affects the small intestine in response to dietary gluten. It is a common cause of malabsorption and affects only genetically predisposed individuals. The immune reaction leads to destruction of the small intestinal villi, starting in the proximal duodenum. Although antibodies are produced as part of the immune reaction, their contribution to the pathogenesis of celiac disease is uncertain.

Testing

Testing should be pursued in patients with typical gastrointestinal symptoms or extraintestinal manifestations and should be considered in those with increased risk (type 1 diabetes mellitus, autoimmune thyroid disease, or a first-degree family member with celiac disease). Gastrointestinal symptoms of celiac disease include chronic diarrhea, bloating, and weight loss as well as constipation and dyspepsia. Other manifestations include iron deficiency anemia, bone loss, abnormal aminotransferase levels, neurologic symptoms, and dermatitis herpetiformis. Patients may also be asymptomatic.

The best initial step is to test for IgA tissue transglutaminase antibodies. Because IgA deficiency is more common in celiac disease, total IgA levels may also need to be measured to prevent false-negative results. In patients with IgA deficiency, testing for anti–deamidated gliadin peptide IgG antibodies or tissue transglutaminase IgG antibodies can be used. Antiendomysial IgA antibodies are highly specific; however, measurement is complex, and testing for these antibodies is generally reserved for situations in which data conflict. Testing for anti-gliadin antibodies (IgA and IgG) should not be used because of low sensitivity and specificity.

Antibody testing is less sensitive if the patient is on a gluten-free diet. In such patients, genetic testing for *HLA-DQ2* or *HLA-DQ8* should be considered. Nearly all patients with celiac disease carry the *HLA-DQ2* or *HLA-DQ8* haplotype; however, up to 40% of the general population carries these mutations. Therefore, genetic testing can rule out but not confirm disease. Among patients with a genetic mutation, gluten can be reintroduced, preferably daily for 1 to 3 months, and serologic testing and/or duodenal biopsy can be performed. Genetic testing may also help rule out disease in patients who did not undergo serologic testing at diagnosis or whose biopsy specimens show histologic changes but negative serologic results.

Diagnosis

Although a markedly elevated (>10 times the upper limit of normal) transglutaminase IgA antibody titer has a positive predictive value for celiac disease approaching 100%, all serologic tests with results positive for celiac disease necessitate upper endoscopy with biopsies from the duodenum to confirm the disease. If clinical suspicion is high and results of initial testing are negative, upper endoscopy and duodenal biopsy can be pursued. There are specific recommendations for the biopsy procedure to minimize false-negative results. Celiac disease is confirmed by increased intraepithelial lymphocytosis and blunting or atrophy of the duodenal villi. If biopsy results suggesting celiac disease are obtained before serologic testing, confirmatory serologic testing should be performed.

Management and Monitoring

Patients with celiac disease should be educated about the gluten-free diet by a knowledgeable registered dietician. Treatment of celiac disease is lifelong avoidance of wheat, rye, and barley, including in patients without symptoms. Patients should know hidden sources of gluten, such as soy sauce (which may contain wheat). Dietary oats are generally safe in celiac disease but should be limited to those with a gluten-free label because cross-contact with gluten-containing grains is possible in some processing settings. Monitoring includes clinical assessment of symptoms and signs of celiac disease, assessment of dietary adherence, and confirmation of normalized antibody levels. Antibody testing may be repeated at 6 and 12 months after diagnosis to assess response to the gluten-free diet and then annually. Repeat upper endoscopy with biopsies should be considered for individuals who have ongoing symptoms while adhering to a gluten-free diet. Assessment of bone density at diagnosis should be considered to ensure adequate bone health.

Nonresponsive Celiac Disease

The most common cause of ongoing celiac disease–related symptoms is continued gluten exposure. When symptoms do not resolve completely with adherence to a gluten-free diet, the accuracy of the diagnosis should be reassessed. Other conditions that may explain ongoing symptoms include IBS, lactose or fructose intolerance, bacterial overgrowth, microscopic colitis, and IBD. Evaluation to exclude these conditions is critical before refractory celiac disease can be diagnosed.

A small number of patients develop refractory celiac disease, in which symptoms of malabsorption and small intestinal inflammation persist despite adherence to a strict gluten-free diet. These patients are typically older than 65 years and present with diarrhea, weight loss, dehydration, and nutritional deficiencies. Possible medication-induced sprue, most commonly olmesartan enteropathy, should be managed by discontinuing the offending medication. Patients with refractory celiac disease should be managed in a specialized celiac disease center.

Dermatitis Herpetiformis

Dermatitis herpetiformis is an extremely pruritic subepidermal autoimmune bullous disease. It typically presents with intensely

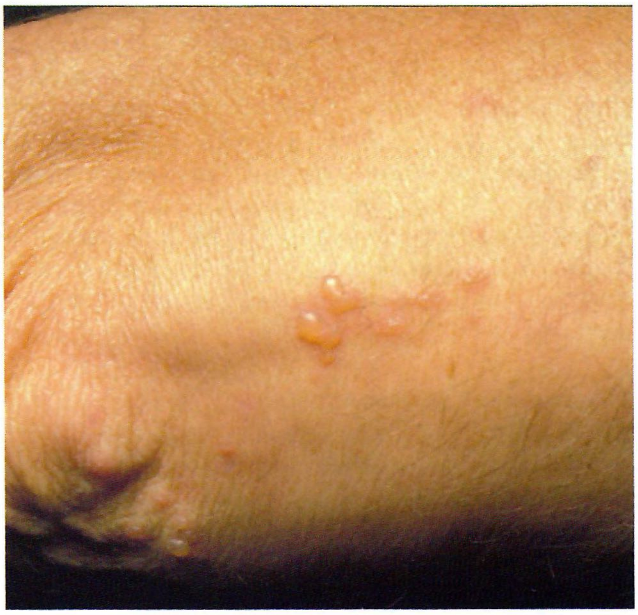

FIGURE 17. Dermatitis herpetiformis, a manifestation of celiac disease, is characterized by pruritic papules and transient, almost immediately excoriated blisters on the elbows, knees, and buttocks.

pruritic papules and fragile vesicles that rapidly break, leaving tiny erosions. The elbows, knees, scalp, and lower back are the most common sites of involvement (**Figure 17**). Most patients have serologic and histologic evidence of celiac disease. Dapsone is quickly effective in inducing a clinical remission, but a gluten-free diet is the preferred long-term management of both the skin and bowel disease. Before initiating dapsone, patients should be tested for glucose-6-phosphate dehydrogenase deficiency.

Nonceliac Gluten Sensitivity

Nonceliac gluten sensitivity is a clinical syndrome of unknown pathophysiology defined by gastrointestinal and extraintestinal symptoms that occur with gluten ingestion and subside with gluten avoidance. By definition, the diagnosis of celiac disease must be excluded. Clinical symptoms of celiac disease and nonceliac gluten sensitivity are indistinguishable. Because gluten-containing foods can also contain nonabsorbable carbohydrates (e.g., fructans), they can cause gastrointestinal symptoms due to osmotic mechanisms as well as fermentation by colonic bacteria. Other than assessing symptom response after withdrawal of gluten, there is no diagnostic test for nonceliac gluten sensitivity; treatment centers on gluten avoidance.

KEY POINTS

- Microscopic colitis is characterized by normal mucosal appearance on endoscopy, with inflammatory changes seen on histopathology; microscopic colitis is not associated with increased risk for colorectal cancer.

(Continued)

KEY POINTS ***(continued)***

- The best initial test for celiac disease is testing for IgA tissue transglutaminase antibodies while the patient is maintaining a gluten-containing diet.
- *HLA-DQ2* or *HLA-DQ8* haplotype is present in nearly all patients with celiac disease, but up to 40% of the general population carries it; thus, genetic testing is most useful in ruling out celiac disease.
- Treatment of celiac disease and dermatitis herpetiformis is lifelong avoidance of wheat, rye, and barley.
- The most common cause of ongoing celiac disease–related symptoms is continued gluten exposure.

Malabsorption

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) is caused by various conditions, including impaired motility, strictures (e.g., in Crohn disease), or blind loops (e.g., small-bowel diverticula). Some evidence suggests that SIBO could contribute to symptoms in IBS-D in the absence of a predisposing structural lesion. Symptoms are often nonspecific and include abdominal discomfort, flatulence, bloating, and diarrhea.

Classically, SIBO is defined by more than 10^5 colony-forming units/mL of jejunal aspirate. Jejunal aspirate is considered the gold standard but is rarely used in clinical practice because of the requirement for endoscopy to obtain cultures, the patchy nature of small intestinal overgrowth, and oropharyngeal contamination of the specimen. Glucose and lactulose breath tests have acceptable specificity (around 80%) but poor sensitivity (30%-40%) for diagnosing SIBO. Diagnosis requires typical symptoms and a confirmatory test (usually breath testing), although empiric antibody therapy with monitoring for symptom relief may be reasonable in patients with a high probability of SIBO. Treatment consists of antibiotics, with courses repeated if the underlying condition cannot be resolved.

Short Bowel Syndrome

Short bowel syndrome is defined by loss of functional small bowel, with resultant loss of absorptive area leading to maldigestion, malabsorption, and malnutrition. Surgery for strangulated bowel, Crohn disease, ischemia, trauma, and obesity can lead to short bowel syndrome.

Treatment centers on ensuring adequate nutrition and depends on degree of intestinal adaptation and whether the patient has an intact ileocecal valve and colon or an ileostomy. Patients with short bowel syndrome and an ileostomy usually require parenteral nutrition and hydration. Patients should be monitored for nutritional deficiencies, and those with extensive ileal resection should be tested for vitamin B_{12} deficiency. Adjunctive therapies include antimotility agents, such as loperamide, and antisecretory drugs, including proton pump inhibitors. Glucagon-like peptide 2 and its analog, teduglutide, may increase intestinal adaptation.

Carbohydrate Malabsorption

Carbohydrates can be classified as monosaccharides (glucose, fructose), disaccharides (lactose, sucrose), oligosaccharides (maltodextrose), or polyols (sorbitol, mannitol). These short-chain carbohydrates are osmotically active and can lead to increased luminal water retention and gas production through colonic fermentation. These actions can cause gastrointestinal symptoms, including gas, bloating, and diarrhea.

Lactose malabsorption is commonly due to loss of the brush-border lactase enzyme in adolescence or adulthood. Fructose malabsorption can also cause gastrointestinal symptoms, such as bloating and diarrhea. Although both lactose and fructose breath tests are available, testing is often not required because symptoms subside with elimination of the sugar from the diet and recur with ingestion of the sugar.

KEY POINTS

- Small intestinal bacterial overgrowth is caused by impaired motility, strictures, or blind loops and is treated with antibiotics.
- Short bowel syndrome is defined by loss of functional small bowel, with resultant loss of absorptive area leading to maldigestion, malabsorption, and malnutrition.
- Lactose malabsorption is common; symptoms occur when lactose is ingested and subside with elimination of lactose from the diet.

Inflammatory Bowel Disease

IBD is an idiopathic chronic inflammatory condition of the gut that includes ulcerative colitis and Crohn disease. Microscopic colitis is considered a type of IBD with distinct clinical and pathologic features. The pathogenesis of IBD likely involves host genetic predisposition and abnormal immunologic responses to endogenous gut bacteria.

Risk Factors

The primary risk factor for IBD is family history, with a risk of approximately 10% for first-degree relatives of affected patients. Individuals of Ashkenazi Jewish descent have increased risk for IBD. Tobacco smoking increases the risk for Crohn disease and is protective for ulcerative colitis.

IBD has a bimodal age presentation: an initial peak incidence in the second to fourth decades of life followed by a less prominent second peak in the seventh and eighth decades.

Clinical Manifestations

Ulcerative Colitis

The major symptoms of ulcerative colitis include diarrhea, abdominal discomfort, rectal bleeding, and tenesmus; symptoms vary by disease extent and severity. Symptoms typically have an insidious onset and often have been present for weeks or months by the time the patient seeks care, although ulcerative colitis may present acutely, mimicking infectious or colonic ischemia.

Rectal inflammation (proctitis) causes frequent defecatory urges and passage of small liquid stools containing mucus and blood. Although bloody diarrhea is considered the hallmark presentation of ulcerative colitis, diarrhea is not always present. Patients with proctitis or proctosigmoiditis may have constipation. Abdominal pain is usually not a prominent symptom of ulcerative colitis; however, most patients with active disease experience vague lower-abdominal discomfort relieved with defecation. Physical examination in patients with mild or moderate ulcerative colitis is usually normal but may reveal mild lower-abdominal discomfort over the affected colonic segment. Fever, nausea, vomiting, or severe abdominal pain indicates a severe attack or complication, such as superimposed infection or toxic megacolon.

Crohn Disease

The clinical presentation of Crohn disease may be subtle and varies by location and severity of inflammation along the gut axis as well as the presence of intestinal complications (e.g., abscess, stricture, or fistula). Abdominal pain is a more common symptom of Crohn disease than of ulcerative colitis. The ileocecal area is the bowel segment most commonly affected by Crohn disease; disease in this area often presents insidiously with mild diarrhea and abdominal cramping. Abdominal examination may reveal fullness or a tender mass in the right hypogastrium. Occasionally, the main presenting symptom is acute right-lower-quadrant pain, mimicking appendicitis. Tenesmus is less common in Crohn colitis than in ulcerative colitis because the rectum is often less inflamed than other colonic segments. Perianal disease is a common presentation of Crohn disease, with anal fissures, ulcers, and stenosis.

Fistulae, a frequent manifestation of the transmural nature of Crohn disease, consist of abnormal connections between two epithelial surfaces (perianal, enteroenteric, enterocutaneous, rectovaginal, enterovesical). Drainage of fecal material from fistulae may lead to passage of feces through the vagina, urethra, or skin. Intra-abdominal abscesses may form; the classic presentation is spiking fevers and focal abdominal tenderness, which may be masked by glucocorticoid use. Strictures may result from fibrosis or severe inflammatory luminal narrowing and may occur in any segment of the gastrointestinal tract, although the terminal ileum is the most common site. Patients with intestinal strictures often initially present with colicky postprandial abdominal pain and bloating that may progress to complete intestinal obstruction.

Table 19 summarizes the features of ulcerative colitis and Crohn disease.

Extraintestinal Manifestations

Inflammatory conditions involving extraintestinal structures may occur with IBD. These manifestations are categorized as

TABLE 19. Features of Ulcerative Colitis and Crohn Disease

Feature	Ulcerative Colitis	Crohn Disease
Depth of inflammation	Mucosa	Transmural
Pattern of disease	Contiguous and symmetric	Skips areas and asymmetric
Location	Colorectum	Mouth to anus
Rectal involvement	Nearly 100%	Less common
Ileal disease	Backwash ileitis (15%)	Common
Fistulas, abscess, and strictures	Rare	Common
Perianal disease	Rare	Common
Granulomas	Unlikely	In approximately 30%
Overt rectal bleeding	Common	Less common
Tobacco use	Protective	Exacerbates

associated with active bowel disease or independent of bowel inflammation. An extraintestinal manifestation occurs in up to 30% of patients with IBD at some time during the disease course. Peripheral arthritis is the most common manifestation (see MKSAP 19 Rheumatology).

The two most common dermatologic manifestations are erythema nodosum and pyoderma gangrenosum, both of which usually correspond to underlying IBD activity. Erythema nodosum most commonly presents as single or multiple tender nodules on extensor surfaces of the lower extremities (**Figure 18**). It usually resolves spontaneously over 4 to 6 weeks. Pyoderma gangrenosum typically presents with an exquisitely tender papule, pustule, or nodule that rapidly develops into an exudative ulcer with undermined and violaceous borders (**Figure 19**). The most frequent location is the lower leg; however, pyoderma gangrenosum is also frequently associated with a stoma site (peristomal) after ostomy placement. It is diagnosed after exclusion of other causes of ulceration. Management of pyoderma gangrenosum includes local wound care, immunosuppressants, and avoiding trauma and surgical debridement because of pathergy (i.e., it occurs at sites of trauma).

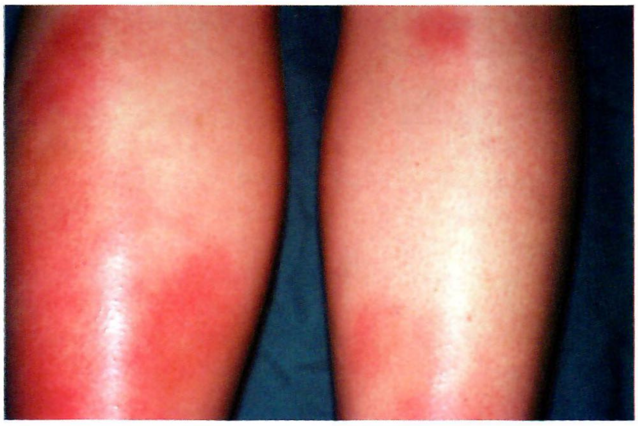

FIGURE 18. Erythema nodosum, a manifestation of inflammatory bowel disease, typically appears as ill-defined erythema overlying subcutaneous, tender nodules most commonly symmetrically located on the anterior shins.

Ocular IBD manifestations include episcleritis and uveitis. Episcleritis is more common and consists of injection of the sclera and conjunctiva. It does not affect visual acuity and is associated with active bowel disease. Uveitis presents with headache, blurred vision, and photophobia. This ocular emergency threatens vision and requires immediate referral to an ophthalmologist. See MKSAP 19 General Internal Medicine 2 for discussion of episcleritis and uveitis. Primary sclerosing cholangitis is the major liver manifestation of IBD, occurring in 5% of patients. Patients most often present with isolated elevations of serum alkaline phosphatase. The liver disease is typically progressive and independent of IBD outcome. See Disorders of the Liver for discussion of primary sclerosing cholangitis.

Diagnosis

Diagnosis of IBD relies on integration of clinical presentation, endoscopic appearance, histologic assessment of mucosal biopsy specimens, radiologic features, and exclusion of

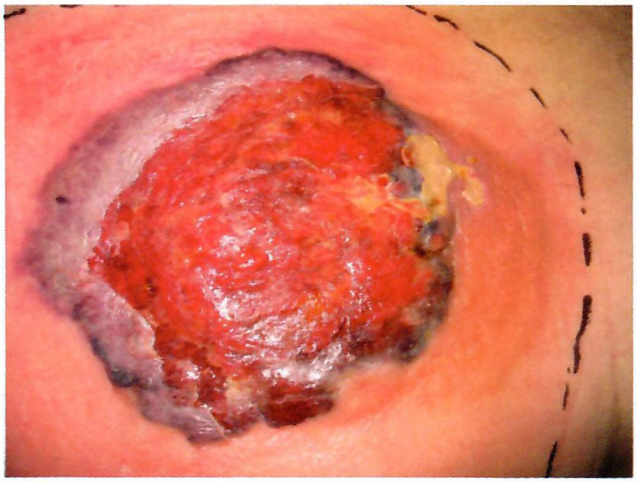

FIGURE 19. Pyoderma gangrenosum, a manifestation of inflammatory bowel disease, typically begins as a small pustule or red nodule that rapidly expands into a painful, exudative wet ulcer with an edematous, infiltrated, actively inflamed border. The border is characteristically violaceous with an edge that overhangs the ulcer.

infectious enteropathogens. IBD should be considered in any patient with chronic or bloody diarrhea. It is paramount to exclude infection, particularly with *C. difficile* and Shiga toxin–producing *E. coli*, by stool tests, especially in patients with acute symptom onset. An elevated fecal calprotectin level may help differentiate IBD from IBS. Antibody tests (e.g., anti-saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies) are available, but their role in diagnosis is undefined; they should not replace endoscopy or biopsy. Laboratory testing helps assess disease activity. Common findings include anemia, thrombocytosis, leukocytosis, and hypoalbuminemia. Iron deficiency anemia often develops from chronic blood loss. Persistently abnormal serum alkaline phosphatase levels should prompt investigation for primary sclerosing cholangitis.

Endoscopy (sigmoidoscopy or colonoscopy) with biopsy is needed to diagnose IBD. Colonoscopy is most commonly used to assess disease extent and severity. At presentation, 50% of patients with ulcerative colitis have disease limited to the rectum and sigmoid (proctosigmoiditis), 20% have left-sided disease (to the splenic flexure), and 30% present with pancolitis (to the cecum). Endoscopic findings range from decreased vascular pattern with erythema and edema in mild disease to large and deep ulcerations in severe disease. Histopathology shows features of chronic colitis, with distorted and branching colonic crypts along with crypt abscesses.

Distribution pattern differs between Crohn disease and ulcerative colitis: 50% of patients have ileocolonic disease; 30%, isolated small bowel disease; and 20%, colonic disease. A minority of patients have isolated upper gastrointestinal tract or perianal disease without small-bowel or colonic inflammation. The earliest endoscopic findings of Crohn disease include aphthous ulcers, which can coalesce to form stellate ulcers, and a "cobblestone" mucosal appearance. A characteristic mucosal feature of Crohn disease is the "skip lesion," consisting of affected areas separated by normal mucosa. Granulomatous inflammation is characteristic of Crohn disease but is uncommonly found on mucosal biopsy specimens. Histopathology in small intestinal Crohn disease shows chronic jejunitis or ileitis, and Crohn colitis has histology similar to that of ulcerative colitis, except for granulomas.

Imaging establishes the location, extent, and severity of IBD. Patients with a severe attack of IBD require plain abdominal radiography to assess for a dilated colon (indicating evolving toxic megacolon) or small-bowel obstruction (**Figure 20**). CT or magnetic resonance enterography provides information about location and severity of small-bowel disease and presence of complicating fistula, abscess, or stricture. Video capsule endoscopy is highly sensitive for detecting small inflammatory lesions of the intestine but is not commonly required.

Treatment

Goals of IBD therapy are to induce and maintain remission and prevent disease- and treatment-related complications. Remission is defined by endoscopic healing of bowel mucosa rather than symptom resolution alone. Four categories of drugs are used: 5-aminosalicylates, glucocorticoids, immunomodulators, and biologics. Stratification based on clinical severity is important in guiding IBD management. There are no validated or consensus definitions of mild, moderate, or severe IBD. For this synopsis, mild ulcerative colitis is defined as fewer than four bowel movements per day, mild to moderate rectal bleeding, no constitutional symptoms, and low overall inflammatory burden. Severe ulcerative colitis is marked by more than six bloody stools per day plus signs of systemic toxicity (e.g., fever, tachycardia, and leukocytosis). Mild Crohn disease is characterized in patients who are ambulatory and are eating and drinking normally, with weight loss less than 10% and no disease-related complications, although patients may have diarrhea and abdominal pain. Patients with severe Crohn disease may be cachectic, with significant weight loss, and may have disease-related complications. These patients are often hospitalized. Patients with moderate disease lie between the extremes.

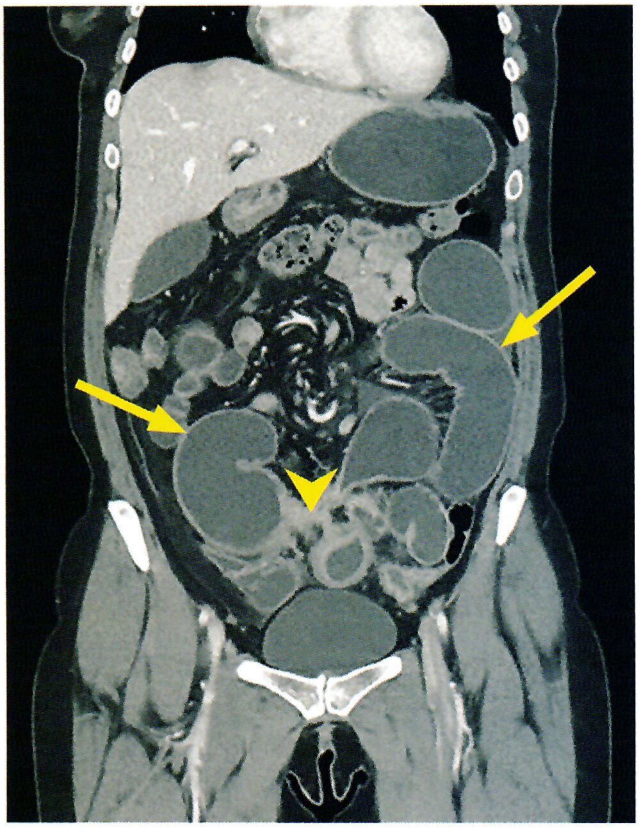

FIGURE 20. CT scan of the abdomen and pelvis in a patient with Crohn disease, showing small-bowel obstruction with dilated loops of small intestine (*arrows*) and matted loops of bowel (*arrowhead*) in the pelvis.

Patients with IBD have markedly increased risk for venous thromboembolism. Hospitalized patients with IBD should receive venous thromboembolism prophylaxis with subcutaneous heparin unless massive gastrointestinal bleeding is present. In such cases, mechanical prophylaxis should be used.

TABLE 20. Medical Treatment of Inflammatory Bowel Disease

Disease Activity	Ulcerative Colitis	Crohn Disease
Mild	Oral and topical 5-ASAs[a] Steroid suppository and enema[b] Multimatrix budesonide	Sulfasalazine for colitis[a] Budesonide for ileocolonic disease[b]
Moderate	Oral and topical 5-ASAs[a] Azathioprine/6-mercaptopurine[c] Multimatrix budesonide and oral glucocorticoids[b] Biologic agents (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab)[a] Tofacitinib[a]	Oral and intravenous glucocorticoids[b] Budesonide for ileocolonic disease[b] Azathioprine/6-mercaptopurine[c] Methotrexate[c] Biologic agents (infliximab, adalimumab, certolizumab, vedolizumab, natalizumab, ustekinumab)[a]
Severe	Oral or intravenous glucocorticoids[b] Cyclosporine[b] Biologic agents (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab)[a] Tofacitinib[a]	Oral or intravenous glucocorticoids[b] Biologic agents (infliximab, adalimumab, certolizumab, vedolizumab, natalizumab, ustekinumab)[a]

5-ASA = 5-aminosalicylate.

[a] Remission and maintenance.

[b] Remission.

[c] Maintenance, glucocorticoid-sparing.

Table 20 summarizes medical treatment of ulcerative colitis and Crohn disease.

Pharmacotherapy for Ulcerative Colitis

5-Aminosalicylates

5-Aminosalicylates (5-ASAs) are believed to have an anti-inflammatory mechanism of action. Unconjugated 5-ASA (mesalamine) is rapidly absorbed in the jejunum, allowing only 20% of the drug to reach the ileum and colon. Oral 5-ASA is modified to reduce upper gastrointestinal absorption and enhance drug delivery to the colon (olsalazine, balsalazide).

The main therapeutic 5-ASAs are sulfasalazine, olsalazine, balsalazide, and delayed- and controlled-release mesalamine. Sulfasalazine has the most adverse effects, including fever, rash, nausea, and headache, and requires concomitant folate supplementation. Sulfasalazine is not considered first-line therapy but is a reasonable choice in patients already taking it who are in remission or have prominent arthritic symptoms.

5-ASAs are the mainstay of treatment of mild to moderate ulcerative colitis, with a dose-dependent response when used to induce remission. Patients with proctitis should receive 5-ASA suppositories. Patients with left-sided disease should receive 5-ASA enemas. In mild to moderate ulcerative colitis, combined 5-ASA therapy (oral and topical) is superior for inducing remission compared with oral or topical therapies alone. 5-ASAs are effective in maintaining remission.

Glucocorticoids

Oral and intravenous glucocorticoids are commonly used to treat moderate to severe flares of ulcerative colitis and can induce remission. However, glucocorticoids are not effective for maintenance therapy and have significant adverse effects. Multimatrix budesonide is a colonic delivery system that allows directed therapy throughout the colon with fewer systemic side effects given its high first-pass hepatic metabolism. It induces remission in mild to moderate ulcerative colitis unresponsive to 5-ASAs and in moderate to severe disease.

Immunomodulators

Thiopurines (azathioprine and mercaptopurine [6-MP]) are immunomodulators used as glucocorticoid-sparing agents in ulcerative colitis. They have a slow onset of action (2-3 months), and patients require a tapering glucocorticoid regimen to bridge the interval until thiopurines take effect. Thiopurines are no more effective than placebo in inducing remission. Thiopurine methyltransferase, a key enzyme in the metabolism of azathioprine and 6-MP, exhibits a population polymorphism. Before initiation of thiopurines, testing for the *TPMT* genotype or phenotype (enzyme activity) is recommended to prevent bone marrow toxicity by identifying individuals with low or absent *TPMT* enzyme activity. However, all patients taking thiopurines require monitoring with complete blood counts and liver chemistry testing because 70% of patients who develop leukopenia while using these agents do not have *TPMT* mutations.

Azathioprine and 6-MP are effective in maintaining remission in ulcerative colitis, should be considered in glucocorticoid-dependent patients, and can be combined with biologic agents. This includes patients who require two courses of glucocorticoids for induction of remission within 1 year and patients who require intravenous glucocorticoids for acute disease flare. The immunomodulator methotrexate is not effective in ulcerative colitis.

Biologic Agents

Tumor necrosis factor (TNF)-α, a proinflammatory cytokine, plays a critical role in the pathogenesis of IBD. The anti-TNF agents infliximab, adalimumab, and golimumab induce and maintain remission in moderate to severe ulcerative colitis, with infliximab being the preferred initial agent. Early use of biologics is appropriate after failure of 5-ASA treatment. Infliximab is administered by intravenous infusion; adalimumab and golimumab are given subcutaneously. Combination therapy with biologics and immunomodulators (thiopurines or methotrexate) is more efficacious than monotherapy with either agent in achieving glucocorticoid-free remission and mucosal healing. Before initiating anti-TNF agents, patients should undergo testing for latent tuberculosis because of an increased risk for tuberculosis reactivation during therapy. Those with latent tuberculosis should receive treatment before or with anti-TNF therapy initiation. Patients should also be assessed for chronic hepatitis B virus infection before starting anti-TNF therapy and receive treatment if needed.

Ustekinumab, a monoclonal antibody that blocks the biologic activity of interleukin-12 and -23 by inhibiting receptors for these cytokines on T cells, is effective in inducing and maintaining remission in patients with moderate to severe ulcerative colitis. Vedolizumab is also effective in inducing and maintaining remission in moderate to severe ulcerative colitis as well as in inducing remission when anti-TNF agents have failed. As with vedolizumab, the small-molecule Janus kinase inhibitor tofacitinib is effective as primary therapy in inducing and maintaining remission in moderate to severe ulcerative colitis and as secondary therapy when anti-TNF agents have failed.

Cyclosporine

Cyclosporine is an immunosuppressive used as an induction agent in select hospitalized patients with severe ulcerative colitis that is unresponsive to intravenous glucocorticoids. It acts as a potential bridge therapy to a slower-onset immunomodulatory or biologic agent.

Pharmacotherapy for Crohn Disease

5-Aminosalicylates

5-ASAs are not efficacious in small-bowel Crohn disease, but sulfasalazine is effective for remission and maintenance therapy for mild to moderate colonic Crohn disease.

Glucocorticoids

Oral and intravenous glucocorticoids are commonly used to treat moderate to severe flares of Crohn disease and are effective in inducing remission. However, as with ulcerative colitis, glucocorticoids are not effective for maintenance therapy. Controlled-release budesonide is effective in inducing remission in mild to moderate ileocolonic Crohn disease.

Immunomodulators

Thiopurines are also used in Crohn disease as steroid-sparing therapy but are not effective in inducing remission. Methotrexate should be considered for alleviating signs and symptoms of steroid-dependent Crohn disease and for maintaining remission. Side effects of methotrexate include hepatotoxicity and interstitial pneumonitis, which can manifest with cough and dyspnea of insidious onset; concomitant folate administration is also necessary.

Biologic Agents

The anti-TNF agents infliximab, adalimumab, and certolizumab treat moderate to severe Crohn disease resistant to glucocorticoids or immunomodulators. Combination therapy with infliximab and azathioprine is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing. Increasing evidence supports biologic agents early in the disease.

The antiadhesion agents vedolizumab and natalizumab are effective in inducing and maintaining remission of moderate to severe Crohn disease. Natalizumab, however, should be used to maintain natalizumab-induced remission of Crohn disease only if serum antibody to JC virus is negative because of risk for progressive multifocal leukoencephalopathy (a central nervous system demyelinating infection caused by reactivation of the JC virus). Testing for anti–JC virus antibody should be repeated every 6 months and treatment stopped if the result is positive. Ustekinumab, a monoclonal antibody that blocks the biologic activity of interleukin-12 and -23 by inhibiting receptors for these cytokines on T cells, is also efficacious in severe Crohn disease, including when anti-TNF therapies prove ineffective.

Medical Therapy for Fistulizing Disease

Fistulizing Crohn disease is difficult to manage. The most appropriate therapy requires expert evaluation and coordination of care between internal medicine and surgery. As part of multimodality therapy, metronidazole and ciprofloxacin may be effective in simple perianal fistula. Infliximab can be effective for perianal, enterocutaneous, and rectovaginal fistulae, and tacrolimus can be effective for perianal and cutaneous fistulae. The combination of infliximab and antibiotics is more effective than infliximab alone for perianal fistulae.

Surgery

In patients with ulcerative colitis, total proctocolectomy with end-ileostomy or ileal pouch-anal anastomosis is performed for medically refractory disease, toxic megacolon, or carcinoma.

Indications for surgery in Crohn disease include medically refractory fistula, fibrotic stricture with obstructive symptoms, symptoms refractory to medical therapy, and cancer. The guiding principle of surgery in Crohn disease is preservation of bowel length and function because disease frequently recurs after segmental resection. Patients with Crohn disease who undergo surgery require aggressive anti-TNF and/or immunomodulator treatment to decrease the rate of postoperative disease recurrence.

IBD Management in Pregnancy

Most medications used to treat IBD are safe in pregnancy. Methotrexate must be stopped at least 3 months before conception because of its teratogenic effects. Biologic agents and thiopurines are considered low risk during pregnancy and breastfeeding and should be continued to maintain disease remission. Although data on tofacitinib in pregnancy are limited, it should be avoided in pregnancy. See MKSAP 19 Rheumatology for a list of biologic agents and associated risks posed in pregnancy.

Health Care Considerations

Patients with IBD have increased risk for vaccine-preventable illnesses. Inactivated vaccines can be safely administered to all patients with IBD, regardless of immunosuppression. Patients with IBD should receive the annual influenza vaccine as well as the COVID-19 vaccine, the 13-valent pneumococcal conjugate vaccine, and the 23-valent pneumococcal polysaccharide vaccine. Ideally, all immunizatons should occur before immunosuppressive therapy begins. Hepatitis B virus vaccination should be considered, especially if biologic therapy is likely to be required. The safety of administering live vaccines to patients with IBD depends on the level of immunosuppression. Certain live vaccines (e.g., measles or herpes zoster) can be given to patients with low-level immunosuppression. Low-level immunosuppression refers to receipt of less than 20 mg of systemic glucocorticoids per day; methotrexate, 0.4 mg/kg or less per week; and azathioprine (≤3 mg/kg per day) or 6-MP (≤1.5 mg/kg per day). Patients receiving anti-TNFs should not be given live vaccines (e.g., measles, mumps, rubella; varicella; and herpes zoster). See MKSAP 19 General Internal Medicine 2 for discussion of vaccination strategies.

All patients with IBD should be encouraged to stop smoking. Smoking increases Crohn disease activity and the risk for extraintestinal manifestations. Smoking cessation may temporarily worsen ulcerative colitis, but overall health benefits exceed this risk. Patients with IBD are at increased risk for metabolic bone disease due to glucocorticoid use and diminished vitamin D and calcium absorption. Bone mineral density testing is recommended in all patients starting oral glucocorticoid therapy. Otherwise, patients with IBD should be screened for osteoporosis based on established guidelines for the general population. See MKSAP 19 General Internal Medicine 2 for discussion of screening for osteoporosis. Patients with IBD should avoid using NSAIDs when possible because these drugs can exacerbate disease activity. Depression and anxiety are more common in patients with IBD than the general population and are associated with medication nonadherence. Therefore, screening for depression and anxiety is recommended in patients with IBD.

Patients with IBD have increased risk for colorectal, cervical, and skin cancers. Some immunosuppressive treatments also increase the risk for cancer, although this risk is outweighed by the protective effect of mucosal healing and resultant reduced risk for cancers associated with chronic mucosal inflammation. Long-standing colorectal inflammation increases cancer risk. In patients with ulcerative colitis with disease proximal to the sigmoid colon (or beyond the rectum, according to some guidelines) or Crohn disease involving more than one third of the colon, surveillance colonoscopy should be done 8 years after diagnosis and every 1 to 3 years thereafter. Primary sclerosing cholangitis increases the risk for colorectal cancer; surveillance colonoscopy should begin at diagnosis and occur yearly thereafter.

Women with IBD have an increased risk for cervical dysplasia; this risk is greater in women using immunosuppressive therapy. Women with IBD receiving immunosuppressive therapy should undergo Pap testing annually and receive human papillomavirus vaccination according to established guidelines.

Patients with IBD also have an increased risk for melanoma and nonmelanoma skin cancers. Most of the risk is associated with specific treatments, such as anti-TNF agents (melanoma) and immunomodulators (nonmelanoma); however, evidence suggests that the increased risk for melanoma is independent of treatment. Patients with ulcerative colitis and Crohn disease should undergo yearly melanoma screening. In addition, patients receiving immunomodulators (azathioprine and 6-MP) should be screened for nonmelanoma squamous cell cancer while using these agents. All patients with IBD should use sunscreen, wear protective clothing, avoid tanning beds, and undergo dermatologic surveillance.

KEY POINTS

- Combined oral and topical 5-aminosalicylate (ASA) therapy is superior for inducing remission in mild to moderate ulcerative colitis; 5-ASAs are effective in maintaining remission.
- The anti-tumor necrosis factor agents can induce and maintain remission in moderate to severe inflammatory bowel disease.
- Azathioprine and 6-mercaptopurine are used in inflammatory bowel disease as steroid-sparing therapy; methotrexate can be used in Crohn disease.
- Patients with inflammatory bowel disease have increased risk for colorectal, cervical, and skin cancers.

Constipation

Constipation is common, affecting 20% of the general population. Constipation can present with symptoms such as infrequent, difficult, or incomplete defecation. It can be acute or chronic and secondary or idiopathic. Medications are the most common cause of secondary constipation; other causes include mechanical obstruction, systemic illnesses, altered physiologic states, and psychosocial conditions (**Table 21**).

Once secondary causes have been excluded, chronic constipation is considered functional (idiopathic). Functional constipation is subcategorized as slow transit, normal transit,

TABLE 21. Secondary Causes of Constipation

Medications
Opioids
Antidiarrheals
Anticholinergics (antispasmodics, antiparkinsonian drugs, tricyclic antidepressants, antipsychotics)
Antihistamines
NSAIDs
Iron supplements
Calcium supplements
Bismuth
Antihypertensives (calcium channel blockers, diuretics, clonidine)
Serotonergic antagonists (ondansetron)
Mechanical Causes
Colorectal cancer
Rectocele
Rectal intussusception
Rectal prolapse
Sigmoidocele
Enterocele
Anastomotic stricture
Anal stenosis/stricture
Extrinsic compression from pelvic/abdominal process
Pelvic floor dysfunction
Systemic Illnesses
Endocrinologic
Diabetes mellitus
Hypothyroidism
Panhypopituitarism
Pheochromocytoma
Glucagonoma
Neuropathy/myopathy
Altered Physiologic State
Hypercalcemia
Hypokalemia
Pregnancy
Porphyria
Heavy-metal poisoning (arsenic, lead, mercury)
Psychosocial
Depression
Cognitive impairment
Immobility

or dyssynergic defecation. Slow-transit constipation is the delayed passage of fecal contents through the colon based on objective transit testing (radiopaque marker study, scintigraphy, or wireless motility capsule). In normal-transit constipation, colonic transit times are adequate based on objective transit testing. Dyssynergic defecation (also termed pelvic floor dyssynergia, obstructed defecation, or outlet obstruction) is difficulty with or inability to expel stool due to abnormalities in contraction and/or relaxation of pelvic floor muscles during defecation. Functional constipation can result from slow-transit constipation and coexistent dyssynergic defecation.

Evaluation

A careful history identifies most causes of secondary constipation. The medication history should focus on the temporal relationship between medications and constipation onset. The history should include assessment for alarm features: hematochezia, acute constipation in elderly patients, unintentional weight loss, family history of colorectal cancer, unexplained anemia, and age older than 50 years with no previous colonoscopy. Anorectal examination, including digital examination during the Valsalva maneuver, is important because it may identify anatomic or functional causes of an evacuation disorder.

Flat-plate radiography of the abdomen is the most useful initial study because it can assess for the presence and distribution of excessive stool in the colon and/or rectum. Colonoscopy indications include blood in the stool, a sudden change in bowel habits, or unexplained anemia. It is also used for colon cancer screening in patients at average and increased risk due to family history of colorectal cancer. Additional imaging or laboratory studies should be considered only if clinically indicated. Physiologic testing, including colon transit testing, anorectal manometry, balloon expulsion testing, or defecography, is reserved for patients with symptoms that do not respond to laxative therapy.

Management

Treatment strategies that may be beneficial when lifestyle and dietary interventions have been ineffective include bulking agents, stimulant laxatives, osmotic laxatives, secretagogues, and/or biofeedback (**Table 22**). The evidence for efficacy is strongest for polyethylene glycol, lubiprostone, and linaclotide. Fiber supplements, polyethylene glycol, magnesium, senna, docusate, and bisacodyl are available without a prescription. For refractory constipation, combination therapy should include agents with different mechanisms of action, such as an osmotic plus a stimulant laxative. For the management of opioid-induced constipation, see MKSAP 19 General Internal Medicine 1.

KEY POINTS

- The most common cause of secondary constipation is medication.
- Treatments include dietary and lifestyle modification, addressing causes of secondary constipation, and various pharmacologic agents.

TABLE 22. Treatments for Constipation

Intervention	Mechanism of Action	Considerations
Bulk Laxative Soluble fiber (psyllium, methylcellulose, calcium polycarbophil, wheat dextrin) Insoluble fiber (bran, rye, flaxseed)	Increases ability of stool to retain water Bulks stool Speeds movement of stool through colon	Start with a low dose and increase slowly Soluble fiber works better than insoluble fiber Bloating, distention, flatulence, and cramping may be limiting
Stool Softener Docusate sodium, docusate calcium	A detergent that allows water to penetrate the stool	Minimal effectiveness in clinical trials Only role is in mild constipation symptoms Well tolerated Few side effects
Osmotic Laxative Polyethylene glycol 3350 Lactulose Magnesium hydroxide/magnesium citrate Sorbitol	Poorly absorbed compounds Creates an osmotic gradient Water moves into the bowel lumen	Polyethylene glycol 3350 and lactulose improve stool frequency and consistency; others have not been tested in clinical trials Bloating and gas can be limiting Caution with use of magnesium in renal insufficiency
Stimulant Laxative Anthraquinones (senna, cascara) Diphenylmethanes (bisacodyl, sodium picosulfate)	Irritates the colon wall, increasing contractions Stimulates sensory nerves lining the colon May inhibit water absorption in the colon	Quickest acting (works in 8-12 hours of ingestion) Senna can cause melanosis coli (benign pigmentation of the colon) Diarrhea, cramping, bloating, and nausea can be limiting
Secretagogue Lubiprostone Linaclotide Plecanatide	Lubiprostone activates type 2 chloride channels on enterocytes lining the gut lumen, causing chloride ions to move into the colonic lumen with sodium and water following the ionic gradient Linaclotide and plecanatide activate guanylate cyclase C receptors on enterocytes, leading to chloride channel activation through a series of processes within the cell	Lubiprostone improves stool form and frequency, straining, and abdominal pain; nausea is a common side effect Linaclotide and plecanatide improve stool form and frequency, straining, bloating, and abdominal pain; diarrhea is a common side effect
Serotonergic Agent Prucalopride	Increases intestinal contractions Increases intestinal secretion	Approved for chronic idiopathic constipation
Neuromuscular Re-education (biofeedback)	Retrains the skeletal muscle involved in defecation (abdominal wall, pelvic floor, anorectal) Corrects altered rectal sensation	Effective for dyssynergic defecation Requires a specially trained physical therapist

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a heterogeneous group of functional bowel disorders defined by abdominal pain in association with defecation and/or change in bowel habits. Pain may worsen or subside with defecation. Altered bowel habits may include constipation, diarrhea, or both. Other common symptoms include abdominal bloating and abdominal distention. IBS is associated with diverse pathophysiologic mechanisms, including increased colonic transit, abnormal intestinal or colorectal sensation, increased colonic bile acid concentration, and epithelial barrier dysfunction. IBS is more common in women and adults younger than 50 years and is frequently associated with psychosocial disturbance. No reliable biomarkers define IBS.

Evaluation

Diagnosis of IBS is no longer one of exclusion but instead can reliably be made by clinical criteria in the absence of alarm features. Diagnosis requires recurrent abdominal pain at least 1 day a week for 3 months along with at least two of the following: defecation-related pain, change in stool frequency, or change in stool consistency. IBS can be further subtyped into IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits, or IBS unclassified. Evaluation for IBS relies on a comprehensive history and physical examination. In patients with IBS-D, stool testing for giardiasis, testing for celiac disease, and fecal calprotectin testing to differentiate from IBD is recommended.

Management

IBS management includes lifestyle modification, changes in diet, probiotics, pharmacotherapy, and cognitive behavioral therapy. Limited evidence suggests that exercise, stress management, and correction of impaired sleep can alleviate IBS symptoms. Evidence is mixed on the effectiveness of probiotics for IBS-D, and this remains an area in need of rigorous clinical trials.

The most common dietary intervention is to increase fiber through diet or fiber supplements. Water-soluble fiber supplements, such as psyllium, are more effective than insoluble dietary fiber, such as bran. Dietary restrictions can include avoiding trigger foods; gluten (in the absence of celiac disease); dairy products; and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) (see Table 18). Because these substances are poorly absorbed in the small intestine, they induce osmotic effects or are fermented in the colon, leading to decreased stool consistency and bloating. Some studies show that 20 to 60 minutes of moderate to vigorous physical activity 3 to 5 days per week improves IBS symptom scores. If fiber supplementation, diet manipulations, and exercise fail to relieve symptoms, medications are used. Evidence supporting the various agents varies; few rigorous studies show long-term effectiveness.

Therapy for Irritable Bowel Syndrome With Predominant Constipation

Several peripherally acting medications are efficacious for treating IBS-C, including polyethylene glycol and intestinal secretagogues (see Table 22). The three intestinal secretagogues for IBS-C are lubiprostone, linaclotide, and plecanatide and are typically used to treat symptoms refractory to osmotic laxatives. Probiotics have uncertain benefit and should be used in the context of a clinical trial.

Therapy for Irritable Bowel Syndrome With Predominant Diarrhea

FDA-approved prescription medications for treatment of IBS-D include rifaximin, eluxadoline, and alosetron. A 14-day course of rifaximin (a nonabsorbable antibiotic) relieves global symptoms, bloating, and loose stools associated with IBS-D for up to 10 weeks after treatment. Re-treatment of patients with recurring IBS-D relieves abdominal bloating and improves stool consistency for 4 weeks after treatment.

Eluxadoline (a combination of a κ- and μ-opioid receptor agonist and a δ-opioid receptor antagonist) relieves diarrhea and abdominal pain in adults with IBS-D. Adverse effects are mainly nausea and headache. Rare cases of pancreatitis and sphincter of Oddi spasm have been reported. Eluxadoline is contraindicated in patients without a gallbladder and those with known or suspected biliary obstruction, sphincter of Oddi disease or dysfunction, ingestion of three or more alcoholic beverages a day, history of pancreatitis or structural disease of the pancreas, severe hepatic impairment, or history of severe constipation.

Alosetron (a selective 5-HT_3 antagonist) is recommended for women with refractory IBS-D; it alleviates abdominal pain and global symptoms. Because of the risk for severe constipation and colonic ischemia, prescribers must be enrolled in an FDA-mandated risk evaluation and mitigation strategy program in order to prescribe alosetron.

Other medications with clinical evidence for treatment of IBS-D include loperamide, antispasmodics, tricyclic antidepressants, and bile acid sequestrants. Loperamide, an opioid receptor agonist, slows colonic transit and increases fluid absorption. It reduces stool frequency and improves stool consistency in IBS-D but does not alleviate abdominal pain. Antispasmodics (e.g., dicyclomine and peppermint oil) decrease abdominal pain and global symptoms of IBS. Tricyclic antidepressants modestly relieve the abdominal pain and global symptoms of IBS-D. The mechanism of action of tricyclic antidepressants in IBS may include reduced activation of pain centers in the brain and peripheral mechanisms that affect pain sensation. Approximately 25% of patients with IBS-D have evidence of bile acid malabsorption; a bile acid binder, such as colesevelam, reduces stool frequency and improves stool consistency in these patients. Psychological therapies (e.g., cognitive behavioral therapy, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy) are beneficial in the treatment of IBS.

KEY POINTS

- Diagnosis of irritable bowel syndrome (IBS) requires recurrent abdominal pain at least 1 day a week for 3 months along with at least two of the following: defecation-related pain, change in stool frequency, or change in stool consistency.
- In patients with IBS with predominant diarrhea, stool testing for giardiasis, testing for celiac disease, and fecal calprotectin testing to differentiate from inflammatory bowel disease is recommended.
- Initial treatment of IBS includes water-soluble fiber supplements, avoiding trigger foods (i.e., gluten and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), and exercise.
- Pharmacotherapy should target predominant symptoms and be used if conservative treatment is not effective.

Centrally Mediated Abdominal Pain Syndrome and Narcotic Bowel Syndrome

Centrally mediated abdominal pain syndrome (CAPS) results from central sensitization with disinhibition of pain signals. When abdominal pain is the primary symptom and is unrelated to food intake and defecation, CAPS should be considered. The abdominal pain is described as constant, nearly constant, or frequently recurring; is not localized; and may include extraintestinal symptoms, such as musculoskeletal pain. It can be associated with impairment in activities of daily living and psychosocial issues. Limited evaluation is needed for patients with chronic pain meeting CAPS diagnostic criteria. Initial evaluation should include a detailed medical and psychosocial history, physical examination, and limited laboratory studies to exclude gastrointestinal bleeding and inflammation.

Successful treatment depends on the patient-physician relationship and should focus on setting appropriate goals and expectations. A combination of pharmacologic and/or psychological therapies may be needed, including tricyclic antidepressants, selective serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors. Four classes of psychotherapy have shown benefits in CAPS when combined with medical therapy: cognitive behavioral therapy, psychodynamic-interpersonal therapy, mindfulness- and acceptance-based therapy, and hypnotherapy.

Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is characterized by the paradoxical increase in abdominal pain with increasing doses of narcotics despite clinical evidence showing improvement or stability of the underlying condition. Patients with this condition often fear tapering off narcotics, believing that the narcotics are "the only thing that helps." The only treatment is complete detoxification and cessation of narcotic use. Enrollment in a supervised detoxification program is recommended.

KEY POINTS

- Centrally mediated abdominal pain syndrome should be considered when abdominal pain is the primary symptom and is unrelated to food intake and defecation; the abdominal pain is described as constant, nearly constant, or frequently recurring; is not localized; and may include extraintestinal symptoms.
- HVC Evaluation for centrally mediated pain syndrome requires a detailed medical and psychosocial history and physical examination, with limited laboratory testing.
- Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is characterized by the paradoxical increase in abdominal pain with increasing doses of narcotics.

Diverticular Disease

A diverticulum is herniation of the mucosa and submucosa through a weakness in the muscle wall. Diverticulosis (presence of diverticula) is the most common finding identified during colonoscopy. The mechanism is thought to involve diet, microbiota, genetics, and colonic motility. Diverticulosis incidence continues to rise in the Western world and increases with age, with a reported prevalence of 80% in persons age 85 years and older. Most patients with diverticulosis are asymptomatic, but 15% develop complications, including bleeding and diverticulitis.

Diverticulitis results from a diverticulum becoming blocked, trapping of bacteria, and development of inflammation. Diverticulitis can be classified as uncomplicated or complicated. Complicated diverticulitis is marked by abscess, fistula, obstruction, or perforation. In some patients, a focal area of colitis can develop in a segment of diverticulosis, called segmental colitis associated with diverticulosis.

The clinical presentation of uncomplicated diverticulitis is colicky abdominal pain relieved with flatus or a bowel movement. On physical examination, abdominal tenderness (usually in the left lower quadrant) is often present. Patients with colovesical fistula may present with dysuria, urinary frequency, pneumaturia, fecaluria, and recurrent urinary infection. Patients with diverticulitis uncommonly present with rectal bleeding.

Acute diverticulitis is often a clinical diagnosis, usually not requiring imaging. However, CT may be performed to assess for an alternative diagnosis or suspected complicated disease (e.g., abscess).

Uncomplicated diverticulitis is usually treated with oral antibiotics (ciprofloxacin or metronidazole) and a liquid diet. Close observation without antibiotics may be considered in some patients. Intravenous antibiotics and hospitalization are required in patients unable to tolerate an oral diet; patients with severe comorbidities, advanced age, or immunosuppression; and patients for whom oral antibiotics have been ineffective.

Treatment of complicated diverticulitis depends on illness severity and CT findings. If the CT scan shows a large (>3 cm) abscess, CT-guided drainage may be needed. Surgery is indicated for patients who present with or develop peritonitis, perforation, obstruction, or persistent sepsis.

A high-fiber diet is recommended to prevent recurrent diverticulitis. No evidence supports restricting such foods as nuts, berries, and seeds to prevent recurrent diverticulitis. Unless performed within the prior year, colonoscopy should be completed in all patients after symptoms resolve to rule out concomitant malignancy.

KEY POINTS

- Acute diverticulitis is often a clinical diagnosis, usually not requiring abdominal imaging unless an alternative diagnosis or complicated disease is suspected. HVC
- Uncomplicated diverticulitis is usually treated with oral antibiotics (ciprofloxacin or metronidazole) and a liquid diet.
- Intravenous antibiotics and hospitalization are required in patients with uncomplicated diverticulitis unable to tolerate an oral diet; patients with severe comorbidities, advanced age, or immunosuppression; and patients for whom oral antibiotics have been ineffective.

TABLE 23. Gastrointestinal Ischemic Syndromes

Problem	Cause	Symptoms	Diagnosis	Treatment
Acute mesenteric ischemia	Arterial embolus (most common)	Severe periumbilical pain; pain is out of proportion to exam	CT mesenteric angiography	Urgent laparotomy if peritoneal signs; embolectomy or thrombectomy
Chronic mesenteric ischemia	Mesenteric atherosclerosis	Postprandial pain, sitophobia, weight loss	CT or MR mesenteric angiography	Angioplasty with stenting or surgical bypass
Colonic ischemia	Low-flow states or drugs	Mild-to-moderate left-lower-quadrant pain and bloody diarrhea	Abdominal CT; colonoscopy with biopsy: segmental mucosal injury	Supportive care with intravenous fluids and bowel rest

Ischemic Bowel Disease

Ischemic bowel disease represents a decrease in blood flow to the small or large intestine that is insufficient to meet intestinal cellular metabolic function. It represents a spectrum of conditions that can be related to acute or chronic alterations of arterial or venous intestinal blood flow. Ischemic bowel disease can be broadly subcategorized into three major clinical syndromes: acute mesenteric ischemia, chronic mesenteric ischemia, and colonic ischemia (**Table 23**).

Acute Mesenteric Ischemia

Clinical Features

Acute mesenteric ischemia (AMI) is a rare condition caused by an abrupt decrease in blood flow to the small intestine that can be obstructive or nonobstructive. Obstructive causes of AMI include cardiogenic emboli or thrombosis related to underlying atherosclerotic disease. Nonobstructive AMI is most commonly caused by vasoconstriction of the mesenteric vasculature in the setting of severe sepsis or marked reduction in effective circulating volume (low-flow states). Mesenteric vein thrombosis may also cause AMI and often is associated with malignancy, hypercoagulable states, or intra-abdominal inflammatory conditions. Bowel infarction occurs with prolonged reduction of blood flow; this is the most important prognostic factor for adverse outcome.

AMI commonly presents with abrupt onset of severe, constant periumbilical abdominal pain followed by the urge to defecate along with loose nonbloody stools. Hematochezia occurs in a minority of cases of AMI (15%), and its presence signifies concomitant right colon ischemia. Although patients report severe abdominal pain, the abdominal examination in early disease is unimpressive and shows no peritoneal signs (pain out of proportion to physical examination findings). This should immediately raise suspicion of early AMI. With delayed or late presentation, intestinal ischemia progresses to infarction, and the mortality rate is high.

Diagnosis

Laboratory and abdominal imaging findings in early AMI, before intestinal infarction develops, are nonspecific. Most patients have elevated leukocyte counts. A serum lactate concentration may be normal, and this should not exclude the diagnosis.

CT angiography is recommended for diagnosing AMI. Although magnetic resonance angiography avoids the risks of radiation and contrast exposure, it takes longer and is less sensitive for distal and nonocclusive disease. Duplex ultrasonography is an effective low-cost method for assessing the proximal mesenteric vessels, but adequate ultrasonography often cannot be performed in patients with AMI. The classic angiographic finding is an embolus or thrombus in the superior mesenteric artery.

Treatment

After aggressive fluid resuscitation, abdominal decompression, pain management, and administration of broad-spectrum antibiotics, emergent surgery is indicated if imaging findings signifying mesenteric infarction, such as pneumatosis intestinalis (gas within the intestinal wall) or portal venous gas, are present. Otherwise, angiography with selective catheterization of the mesenteric vessels may be performed along with endovascular intervention if possible. Patients with mesenteric arterial or venous occlusion should begin receiving systemic anticoagulation to prevent thrombus propagation, and anticoagulation should be continued after surgery to prevent additional thrombus formation.

Chronic Mesenteric Ischemia

Clinical Features

Chronic mesenteric ischemia (CMI) is an uncommon condition that involves a gradual decrease in blood flow to the small intestine over months to years. It most commonly results from atherosclerotic narrowing of the mesenteric arteries.

The classic symptom triad of CMI is postprandial abdominal pain, sitophobia (fear of eating), and weight loss. However, this triad is seen in only 30% of patients with CMI, and CMI should be suspected in the setting of recurrent postprandial abdominal pain. Pain begins approximately 30 minutes after food ingestion as the fixed narrowing of the mesenteric arteries prevents blood flow from increasing and meeting the increased functional demand of the small bowel, with resultant ischemia.

Diagnosis

The diagnosis of CMI requires exclusion of alternative causes of postprandial abdominal pain and weight loss along with compatible imaging findings. CT or magnetic resonance angiography findings suggesting CMI include severe stenosis (>70%) of two of the three mesenteric arteries.

Treatment

CMI is treated with percutaneous endovascular stenting or surgical revascularization. Periprocedural morbidity and mortality are lower with endovascular stenting; however, this method is less durable than surgical revascularization.

Colonic Ischemia

Colonic ischemia is the most common form of ischemic bowel disease. It most commonly results from a nonocclusive low-flow state in microvessels, which occurs with hypovolemia or hypotension. Risk factors include age (>60 years), female sex, vasoconstrictive and antihypertension medications, constipation, thrombophilia, and COPD.

Clinical Features

Colonic ischemia presents with the abrupt onset of lower abdominal discomfort that is mild to moderate and cramping, followed within 24 hours by diarrhea and hematochezia. See Gastrointestinal Bleeding for discussion of lower gastrointestinal bleeding.

Diagnosis

Physical examination most commonly reveals mild lower abdominal tenderness over the involved bowel segment without peritoneal signs. Laboratory studies may show mildly elevated leukocyte count and blood urea nitrogen level.

Abdominal CT is indicated to assess the severity, phase, and distribution of colonic ischemia. CT findings in colonic ischemia are nonspecific and include bowel-wall thickening (**Figure 21**) and pericolonic fat stranding (an increase in density within pericolonic fat secondary to inflammation), often in the distribution of the "watershed" areas of the colon (splenic flexure and rectosigmoid junction). Infections that can mimic colonic ischemia, such as with cytomegalovirus, *C. difficile*, and enterohemorrhagic *E. coli*, must be excluded. Colonoscopy with biopsy is the test of choice to confirm the diagnosis of colonic ischemia.

Because colonic ischemia is most commonly caused by a nonocclusive low-flow state, dedicated imaging of the mesenteric vasculature is of low yield and generally not indicated. The exception is right-sided colonic ischemia, which can be the harbinger of AMI caused by a focal thrombus or embolus of the superior mesenteric artery. Therefore, patients with right-sided colonic ischemia require noninvasive imaging of the mesenteric vasculature to exclude an occlusive process of the superior mesenteric artery.

Treatment

Most cases of colonic ischemia are mild and transient, with rapid spontaneous resolution. Patients with more severe disease require hospitalization for supportive care with bowel rest, restoration of intravascular volume, antimicrobial therapy in many cases, and close observation. Only a small percentage of patients require operative intervention for necrotic bowel or irreversible complications, such as stricture.

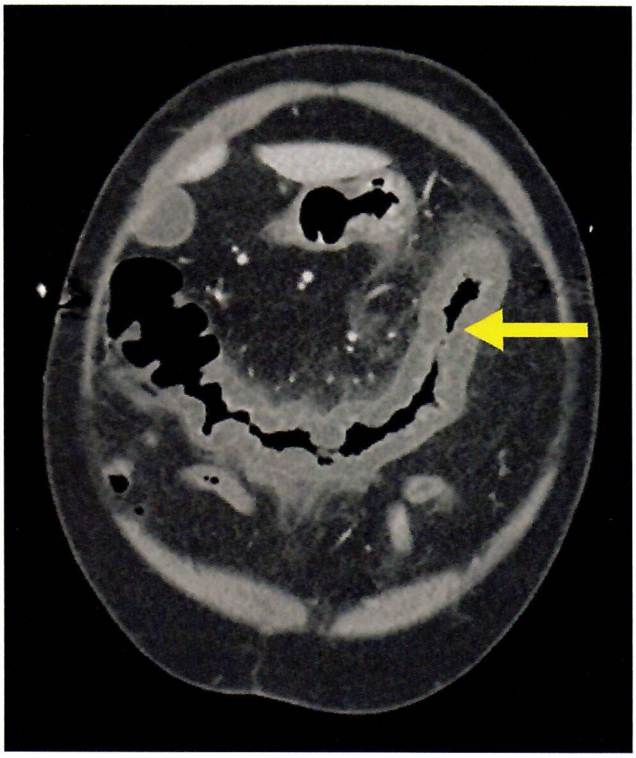

FIGURE 21. CT scan showing colonic ischemia causing segmental thickening (*arrow*) of the transverse colon wall.

KEY POINTS

- Acute abdominal pain out of proportion to physical examination findings should immediately raise suspicion for early acute mesenteric ischemia.
- CT angiography is the recommended method for the diagnosis of acute mesenteric ischemia.
- Chronic mesenteric ischemia should be suspected in the setting of recurrent postprandial abdominal pain.
- Colonic ischemia presents with the abrupt onset of lower abdominal discomfort that is mild to moderate and cramping, followed within 24 hours by diarrhea and hematochezia.

Anorectal Disorders

Perianal Disorders

Perianal symptoms, including bright red blood per rectum, anal pain, anal itching, or a reported anal mass, should prompt a detailed evaluation of the anus, anal canal, and rectum that includes visual inspection of the anus and digital rectal examination. Anoscopy or proctoscopy may be required to establish the diagnosis. Colonoscopy is indicated when additional alarm features are present; these include age older than 50 years, altered bowel habits, anemia, IBD, unexplained weight loss, and/or family history of colorectal cancer.

Hemorrhoids

Risk factors for symptomatic hemorrhoids include ascites, pregnancy, excessive sitting or squatting, systemic rheumatic disorders, low dietary-fiber intake, obesity, and sedentary lifestyle. Recurrent straining and persistent bowel alterations (constipation or diarrhea) can lead to engorgement of hemorrhoid plexuses, causing symptoms of bleeding, prolapse, and swelling. Age-related changes can cause the hemorrhoid beds to slide back and forth during defecation, resulting in mucoid anal discharge, perianal wetness, soiling, irritation, and/or pruritus. Pain is not a common symptom of uncomplicated hemorrhoids and should raise suspicion for hemorrhoid complications, including thrombosis, ischemia, or incarceration from prolapse, or for an alternative diagnosis, such as anal fissure, perirectal infection, or perianal abscess. Hemorrhoids are categorized as internal if proximal to the dentate line, external if distal to the dentate line, or mixed if crossing the dentate line.

Evaluation of hemorrhoids should always include a careful perianal and digital rectal examination. Symptomatic hemorrhoids can be confused with rectal mucosal prolapse, full-thickness rectal prolapse, or a prolapsed rectal polyp. Prolapsed concentric folds indicate rectal prolapse as opposed to a prolapsed hemorrhoid or anal polyp (**Figure 22**). Further direct evaluation of the anorectum can be considered with anoscopy or flexible sigmoidoscopy.

First-line therapy for hemorrhoids includes increased fiber intake, adequate liquid intake, and avoidance of straining. Various topical agents may reduce hemorrhoid symptoms but are not necessary for curative therapy. Patients with internal hemorrhoids unresponsive to medical therapy should be considered for banding. Other options, including sclerotherapy and infrared coagulation, are less effective.

Thrombosed external hemorrhoids are best treated with surgical excision within 72 hours of symptom onset. Surgical hemorrhoidectomy should be reserved for refractory hemorrhoids, large external hemorrhoids, or combined internal and external hemorrhoids with rectal prolapse.

Anal Fissure

Anal fissures are longitudinal mucosal tears in the anal canal characterized by anorectal pain that is worsened by bowel movements and sitting (**Figure 23**). Rectal bleeding with bowel movements or wiping is common. Anal fissures are idiopathic or result from trauma due to passage of hard stool, receptive anal intercourse, or insertion of a foreign body (such as an enema or endoscope). Lateral anal fissures should raise concern for other entities, including Crohn disease, ulcerative colitis, tuberculosis, syphilis, HIV infection, psoriasis, or anal cancer. Anal fissures lasting more than 8 to 12 weeks are considered chronic and may be characterized by edema and

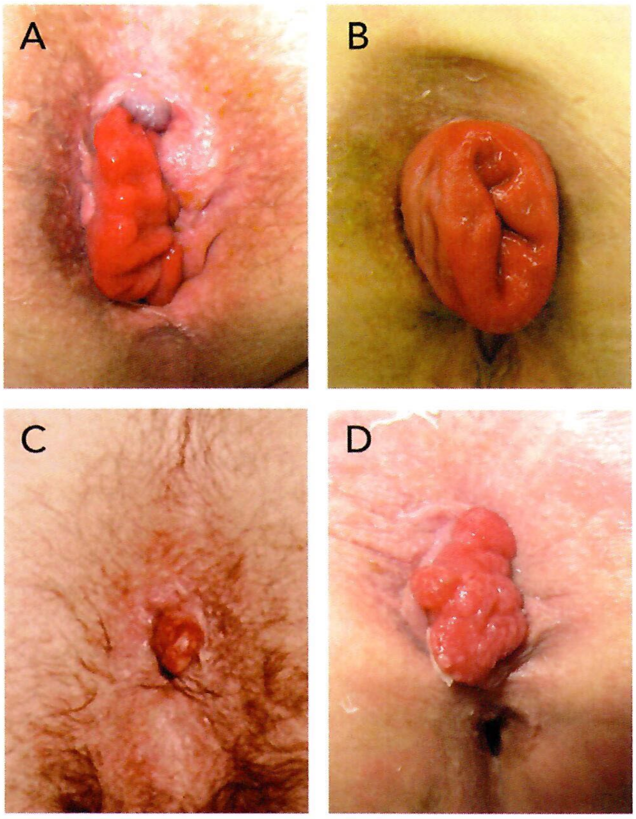

FIGURE 22. Hemorrhoids are vascular cushions that support the muscles of the anal sphincter by swelling up as needed to maintain stool continence. Prolapsed hemorrhoids (**A**) are internal hemorrhoids that protrude out of the rectum. The hallmark of rectal prolapse (**B**) is the identification of concentric rings of the rectum protruding through the anus. Prolapsed polyps (**C, D**) present as mucosa-covered globular masses protruding from the anus.

Images courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

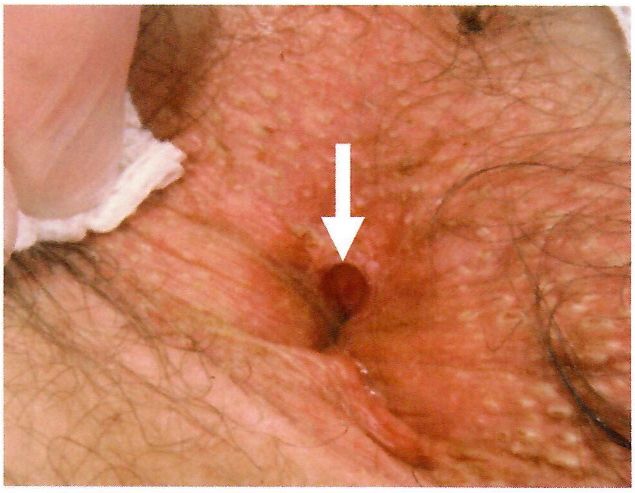

FIGURE 23. Anal fissures are painful longitudinal mucosal tears in the anal canal.

Image courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

fibrosis as well as a sentinel pile (appearing as a skin tag) or hypertrophied anal papilla within the anal canal.

Acute anal fissures generally resolve within a few weeks with the use of sitz baths, psyllium, and bulking agents. Topical anesthetics and anti-inflammatory agents can be considered to address pain or bleeding but are not required to promote fissure healing. Rectal spasm is the major reason for anal fissures becoming chronic and should be treated with topical calcium channel blockers or nitrates. Patients with chronic fissures unresponsive to these measures should be referred for internal sphincter botulinum toxin injection or surgical sphincterotomy.

Fecal Incontinence

Fecal incontinence is recurrent, uncontrolled passage of fecal material of at least 3 months' duration. Fecal incontinence does not include passage of clear mucus or flatus incontinence. Fecal incontinence is grossly underreported because of associated embarrassment; health care providers should inquire about it during clinic visits in patients at risk. Fecal incontinence is more common in multiparous women and in patients with advanced age; obesity; diarrhea or urinary incontinence; or history of obstetric complications, anorectal surgery, or anorectal disease. Factors contributing to fecal incontinence include loose stools, impaired rectal storage capacity, altered rectal sensation, and reduced anal sphincter tone. Constipation with resultant fecal loading and overflow diarrhea can also cause fecal incontinence.

A digital rectal examination is essential in the evaluation. It can identify reduced anal sphincter tone, prolapse of hemorrhoids or rectum, or rectal stool impaction. Additional diagnostic testing is determined by the history and rectal examination. If fecal loading is suspected, an abdominal radiograph can be diagnostic. If diarrhea is present, stool testing and/or colonoscopy should be considered. If weak sphincter tone is appreciated or rectal urgency is reported, evaluation may include neurologic evaluation for spinal cord disorders, anorectal manometry to assess anal sphincter pressure and rectal sensation, anal endosonography for anal sphincter defects, or defecography for structural evaluation of the pelvic floor.

Initial treatment should be directed at reversible factors, such as diarrhea, constipation, offending medications, smoking, obesity, and physical inactivity. Effective dietary modifications include fiber supplementation and avoidance of trigger foods. If there is no response to conservative measures, the next step is pelvic floor muscle training with physical therapists. In cases not responding to biofeedback therapy, other treatment options include anal plugs, anal wicking, minimally invasive procedures (e.g., injectable bulking agents or sacral nerve stimulation), or surgery (e.g., sphincteroplasty).

Anal Cancer

Anal cancer (**Figure 24**) is rare, with a yearly incidence of 8000 cases in the United States. Squamous cell cancer is the most common type, representing 80% of all anal cancers. The incidence has been rising by 2.2% each year for the last decade. Delayed diagnosis by up to 2 years in more than half of cases has resulted in increased need for aggressive surgical intervention.

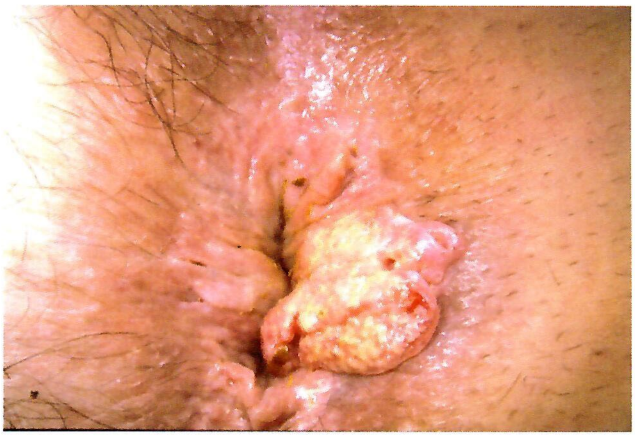

FIGURE 24. Anal cancer presenting as an ulcerated mass protruding from the anal canal. The presentation of anal cancer can vary from an obstructing anal mass to a nonprotruding polyp or flat growth in the anal canal.

Image courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

Human papillomavirus infection and intraepithelial neoplasia are strongly linked with anal cancer. Risk is increased in men who have sex with men and in patients with HIV infection, history of condylomata, or kidney or liver transplantation. Presenting symptoms of anal cancer may include bleeding, pain, or pruritus; however, 25% of cases present without any anorectal symptoms. Rates of anal squamous cell cancer are 1 in 100,000 in patients with IBD or ulcerative colitis and 2 in 100,000 in patients with Crohn disease, largely in those with perianal disease. These statistics warrant heightened vigilance in patients with long-standing perianal disease. Cancer occurs at a young age in patients with Crohn disease (mean age, 42 years), with a typical presentation of anal pain. Anal cancer is aggressive in patients with Crohn disease; most patients require radical surgery, and cumulative overall and disease-free survival is 37% at 5 years.

Although no recommendations address screening for anal dysplasia in at-risk populations, screening modalities include digital rectal examination, an anal Pap test, human papillomavirus testing, and high-resolution anoscopy.

Biopsy is required to diagnose anal cancer.

For treatment and follow-up of anal cancer, see MKSAP 19 Oncology.

KEY POINTS

- First-line therapy for hemorrhoids includes increased fiber intake, adequate liquid intake, and avoidance of straining.
- Initial treatment of fecal incontinence is directed at reversible factors, such as diarrhea, constipation, offending medications, smoking, obesity, and physical inactivity.

(Continued)

KEY POINTS *(continued)*

- Presenting symptoms of anal cancer may include bleeding, pain, or pruritus; however, 25% of cases present without any anorectal symptoms.
- Patients with Crohn disease with long-standing perianal disease are particularly at risk for anal cancer.

Colorectal Neoplasia

Epidemiology

Colorectal cancer is the third most common cancer and second most common cause of cancer-related mortality among men and women in the United States. There are approximately 145,600 new cases in the United States annually, and lifetime risk for colorectal cancer is 4.5% for men and 4.1% for women.

The incidence and mortality for colorectal cancer have decreased over the past 30 years because of changes in risk factors (e.g., decreased smoking) and early detection. However, the number of colorectal cancer cases in patients younger than 50 years has steadily increased for unknown reasons. Survival rates exceed 90% with localized disease, underscoring the importance of early detection. Between 20% and 53% of adults older than 50 years have premalignant colon adenomas detected on screening, and 3% to 8% of the adenomas have advanced histologic features. Despite strong evidence supporting colorectal cancer screening, only about 63% of Americans older than 50 years are up to date for recommended testing.

KEY POINTS

- The number of colorectal cancer cases in patients younger than 50 years is increasing.
- Between 20% and 53% of adults older than 50 years have premalignant colon adenomas detected on screening, but only about 63% of Americans older than 50 years are up to date for recommended screening.

Pathogenesis

Colorectal cancer develops through one of three mechanisms: chromosomal instability, microsatellite instability, and hypermethylation of tumor suppressor genes.

Chromosomal instability is the most common mechanism, accounting for approximately 85% of colorectal cancers. Chromosomal instability is characterized by abnormal cells that gain or lose whole or large fractions of chromosomes (aneuploidy) at an increased rate compared with normal cells. Stepwise accumulation of mutations leads to progression from normal colon to adenoma to cancer. The most commonly mutated gene in this pathway is the adenomatous polyposis coli (*APC*) gene, a multifunctional tumor suppressor gene. *APC* mutations are implicated in the development and spread of colon cancer. Germline mutations in *APC* lead to familial adenomatous polyposis.

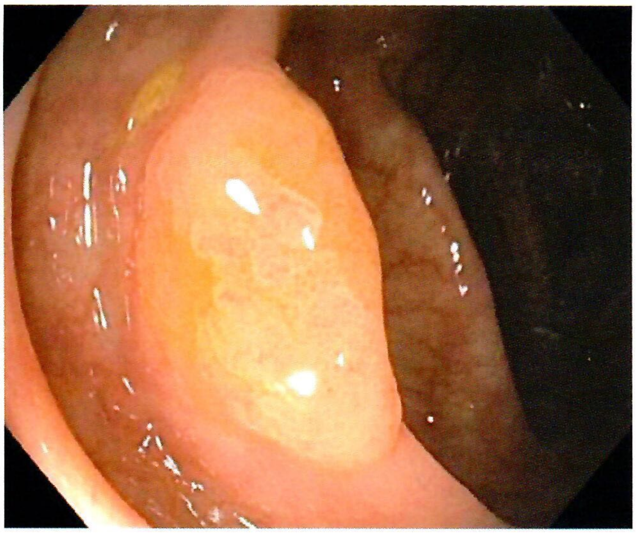

FIGURE 25. A serrated lesion in the ascending colon, showing flat morphology that can make these lesions difficult to identify on colonoscopy.

Microsatellites are dozens to hundreds of repetitive nucleotide sequences seen throughout the human genome. The term *microsatellite instability* refers to mismatched bases at repeated DNA microsatellites. Microsatellite instability accounts for about 15% of colorectal cancers and is characterized by defective DNA mismatch repair, leading to multiple mutations, adenomas, and cancer. Defective mismatch repair can occur if there is a germline mutation in a mismatch repair gene in Lynch syndrome (including *MLH1*, *MSH2*, *MSH6*, and *PMS2*) or in the epithelial cell adhesion molecule gene (*EPCAM*) or as a result of sporadic methylation of the *MLH1* promoter.

The third mechanism involves hypermethylation of tumor suppressor genes and the development of serrated lesions and cancer. Serrated lesions are a heterogeneous group of lesions classified by their sawtooth appearance on histology. They are often found in the proximal colon and may be flat and difficult to distinguish from normal mucosa (**Figure 25**).

KEY POINT

- Colorectal cancer develops through one of three mechanisms: chromosomal instability, microsatellite instability, and hypermethylation of tumor suppressor genes; chromosomal instability is the most common mechanism, accounting for 85% of cases.

Risk Factors

Nonmodifiable risk factors for colon cancer include age (≥50 years), male sex, Black race, and personal or family history of colon adenomas or colorectal cancer. The risk doubles with a family history of colorectal cancer in a first-degree relative.

Long-standing (≥8 years) colonic inflammatory bowel disease (Crohn disease and ulcerative colitis) is associated with about a 2.7-fold increased risk; the risk depends on the severity and extent of bowel involvement. Patients with ureterocolic anastomoses after bladder surgery and adult survivors of childhood malignancy who received abdominal radiation are also at increased risk for colorectal cancer.

Modifiable risk factors include diets high in red and processed meat; low intake of fruits, vegetables, fiber, and dairy; use of alcohol and tobacco; type 2 diabetes mellitus; sedentary lifestyle; and obesity.

KEY POINTS

- Nonmodifiable risk factors for colorectal cancer include age (≥50 years), male sex, Black race, and personal or family history of colorectal cancer.
- Modifiable risk factors for colorectal cancer include diets high in red and processed meat; low intake of fruits, vegetables, fiber, and dairy; use of alcohol and tobacco; type 2 diabetes mellitus; sedentary lifestyle; and obesity.

Chemoprevention

Substantial epidemiologic and experimental data suggest that aspirin prevents colorectal cancer. Cohort and case-control studies, for example, show that aspirin use is associated with a 30% decreased risk for colorectal cancer. Randomized controlled trials, however, have shown that aspirin decreases the risk for recurrent adenomas but has less clear benefit in preventing colorectal cancer. The U.S. Preventive Services Task Force updated their guidelines in 2015 to include the use of low-dose aspirin (81 mg/d) for preventing colorectal cancer and cardiovascular disease in individuals aged 50 to 59 years who are at increased risk for cardiovascular disease, have a life expectancy of 10 years, and are willing to take aspirin for 10 years. See MKSAP 19 General Internal Medicine 2 for a more detailed discussion of aspirin use in primary prevention.

Studies of other NSAIDs for prevention of colon cancer and adenomas have also yielded positive results; however, benefits of aspirin and other NSAIDs must be weighed against harms, especially gastrointestinal bleeding.

Some evidence suggests that selective cyclooxygenase-2 inhibitors prevent recurrent adenomas and decrease the incidence of advanced lesions; however, the associated increased cardiovascular risk confounds a recommendation of their use for chemoprevention.

KEY POINT

- The U.S. Preventive Services Task Force recommends the use of low-dose aspirin for preventing colorectal cancer and cardiovascular disease in individuals aged 50 to 59 years who are at increased risk for cardiovascular disease.

Screening

Screening individuals at average risk is discussed in MKSAP 19 General Internal Medicine 2.

Screening strategies for individuals at increased risk for colorectal cancer are described in **Table 24**.

TABLE 24. Screening for Colorectal Cancer in Individuals at Elevated Risk

Risk Category	Criteria	Screening Recommendations (Age; Modality; Interval)
Increased	Family history of CRC:	
	CRC diagnosed in FDR age <60 years or ≥2 FDRs at any age	Begin at age 40 years or 10 years earlier than age of youngest FDR at diagnosis, whichever comes first; colonoscopy; repeat every 5 years[a]
	CRC diagnosed in FDR age ≥60 years	Begin at age 40 years; any modality; repeat every 10 years[a]
	Personal history of CRC	Perform at time of diagnosis; colonoscopy; repeat at 1 year, 3 years, and, if normal, every 5 years thereafter until risks outweigh benefit of continued screening
	Adult patients with cystic fibrosis	Cystic Fibrosis Foundation recommends beginning CRC screening at age 40 years in individuals with cystic fibrosis, with continued rescreening every 5 years
High	Familial adenomatous polyposis	Begin at age 10-12 years; flexible sigmoidoscopy or colonoscopy; repeat every 1-2 years until colectomy
	Lynch syndrome	Begin at age 20-25 years or 10 years earlier than youngest cancer in family; colonoscopy; repeat every 1-2 years
	Inflammatory bowel disease (Crohn disease or ulcerative colitis)	Begin after 8 years of chronic colitis; colonoscopy with biopsies; repeat every 1-2 years

CRC = colorectal cancer; FDR = first-degree relative (parent, sibling, or child).

[a] If baseline examination is normal.

Data from Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. multi-society task force on colorectal cancer. Gastroenterology. 2017;153:307-323. [PMID: 28600072] doi:10.1053/j.gastro.2017.05.013; Syngal S, Brand RE, Church JM, et al.; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015 Feb;110(2):223-62; quiz 263. [PMID: 25645574]; Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114:384-413. [PMID: 30840605] doi:10.14309/ajg.0000000000000152.

TABLE 25. Classification of Colorectal Polyps

Adenomatous Polyps[a]
Tubular adenoma
Tubulovillous adenoma
Villous adenoma
Serrated Lesions
Hyperplastic polyp
Sessile serrated polyp with or without cytologic dysplasia
Traditional serrated adenoma
Other
Hamartomatous polyp
Inflammatory polyp

[a] With or without high-grade dysplasia.

Because adenomas are an intermediary step in the progression from normal colonic mucosa to colon cancer, identification and management of adenomatous polyps are critical. Adenomas can be found throughout the colon. They are classified by morphology, histology, and degree of dysplasia (**Table 25**). Adenomas with any degree of villous histology or high-grade dysplasia have greater malignant potential. Risk is also increased in polyps larger than 1 cm. The progression of adenoma to carcinoma takes approximately 8 to 10 years.

Key quality indicators for screening colonoscopy include adequate bowel preparation, preparation sufficient to identify polyps 6 mm or larger, visualization of the entire colon to the cecum, adenoma detection rate, and longer duration of colonoscopy.

KEY POINTS

- Screening colonoscopy is recommended to begin at age 40 years or 10 years earlier than the age of the youngest first-degree relative diagnosed with colorectal cancer before age 60 years.
- Colorectal cancer screening is recommended to begin at age 40 years for any patient with two first-degree relatives diagnosed with colorectal cancer after age 60 years.
- Colonoscopy is recommended for patients with Lynch syndrome at age 20 to 25 years or 10 years earlier than youngest age at which cancer was diagnosed in the family.

Clinical Presentation

Colorectal cancer may be asymptomatic or may present with iron deficiency anemia, gastrointestinal bleeding, altered bowel habits, abdominal pain, colonic obstruction, and weight loss in more advanced cases.

Diagnosis and Staging

Colorectal cancer is usually diagnosed by colonoscopy with biopsy. Staging is based on tumor size and extent of invasion into local tissues, lymph node involvement, and evidence of metastasis (TNM system). Cross-sectional imaging of the chest, abdomen, and pelvis is used for staging in the initial evaluation after diagnosis. Management of colon cancer depends on stage, evidence of microsatellite instability, and presence of specific mutations, including *KRAS/NRAS* and *BRAF*.

For staging and treatment of colorectal cancer, see MKSAP 19 Oncology.

Favorable characteristics include stage I to II cancer and lack of angiolymphatic involvement. Endoscopic resection of polyps can be curative, and negative margins after removal are a favorable sign. Malignant sessile or flat polyps are associated with higher risk for recurrence and local or distant spread.

KEY POINTS

- Colorectal cancer is usually diagnosed by colonoscopy with biopsy.
- Cross-sectional imaging of the chest, abdomen, and pelvis is used for staging in the initial evaluation after diagnosis.

Surveillance

Surveillance for colorectal cancer after screening or polypectomy is based on baseline examination findings (**Table 26**).

Hereditary Colorectal Cancer Syndromes

Several hereditary syndromes are associated with colorectal cancer (**Table 27**).

Lynch Syndrome

Lynch syndrome is characterized by germline mutations in the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or the epithelial cell adhesion molecule gene (*EPCAM*), leading to an increased risk for neoplasia of the colon and other organs. The previous name for this syndrome, hereditary nonpolyposis colorectal cancer, is no longer used because the syndrome is associated with colorectal polyps as well as extracolonic cancers. The syndrome follows an autosomal dominant inheritance pattern, and new mutations are rare.

In persons with Lynch syndrome, the lifetime risk for colorectal cancer depends on the location of the gene mutation; the risk can be as high as 50% to 80%. Colorectal cancer in Lynch syndrome is more likely in the proximal colon and can display characteristic pathologic features, such as tumor-infiltrating lymphocytes and medullary growth pattern. Colorectal tumors in Lynch syndrome result from microsatellite instability that can be assessed using polymerase chain reaction or immunohistochemistry (see Pathogenesis). All colorectal cancers should be screened for Lynch syndrome genetic mutations or microsatellite instability.

TABLE 26. Surveillance for Colorectal Cancer After Screening or Polypectomy

Adenomatous Polyps	Interval to Next Colonoscopy
1-2 tubular adenomas <10 mm	7-10 years
3-4 tubular adenomas <10 mm	3-5 years
5-10 tubular adenomas <10 mm, adenoma ≥10 mm, adenoma with villous component, or adenoma with high-grade dysplasia	3 years
≥10 adenomas[a] on single examination	1 year
Piecemeal resection of adenoma ≥20 mm	6 months, then 1 year later, then 3 years after second examination
Serrated Polyps	**Interval to Next Colonoscopy**
≤20 HP in rectum or sigmoid colon <10 or ≤20 HP proximal to sigmoid colon <10 mm	10 years
1-2 SSP <10 mm in size	5-10 years
3-4 SSP <10 mm in size or HP ≥10 mm	3-5 years
5-10 SSP <10 mm in size, SSP ≥10 mm, or SSP with dysplasia	3 years
Serrated polyposis syndrome	1 year

HP = hyperplastic polyps; SSP = sessile serrated polyps; TSA = traditional serrated adenomas.

[a] Consideration for genetic testing based on adenoma burden, age, and family history.

Data from Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-society Task Force on Colorectal Cancer. Gastroenterology. 2020;158:1131-1153.e5. [PMID: 32044092] doi:10.1053/j.gastro.2019.10.026.

Lynch syndrome should be suspected in patients with synchronous (occurring within 6 months of the primary tumor diagnosis) or metachronous (occurring more than 6 months after the primary tumor diagnosis) colorectal cancers, colorectal cancer before age 50 years, occurrence of multiple Lynch syndrome–associated cancers, or a family history of multiple cancers associated with Lynch syndrome. Clinical criteria to evaluate for Lynch syndrome include the Amsterdam and Bethesda criteria (**Table 28**) as well as newer models, such as the PREdiction Model for gene Mutations 5 (PREMM_5). The Amsterdam II criteria are specific but not sensitive for the diagnosis of Lynch syndrome, whereas the Bethesda criteria have good sensitivity but poor specificity. Given the limitations of the clinical criteria and predictive models, genetic counseling and testing should be offered to patients with a personal and/or family history consistent with Lynch syndrome as well as to patients whose tumor shows evidence of microsatellite instability or loss of mismatch repair protein expression. When a mutation is identified in a family, first-degree relatives should be tested and surveillance instituted.

Screening recommendations for colorectal cancer in patients with Lynch syndrome are described in Table 24. Risk-reducing total hysterectomy and bilateral salpingo-oophorectomy should be considered starting at age 40 to 45 years after childbearing is completed in women who carry Lynch syndrome mutations.

Screening with upper endoscopy for stomach and small-bowel cancers can be considered starting at age 30 to 35 years and repeated every 2 to 5 years. Testing and treatment for *Helicobacter pylori* are also recommended in patients at risk for or with Lynch syndrome to decrease the likelihood of gastric cancer.

Adenomatous Polyposis Syndromes

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an inherited disorder characterized by multiple (usually >100) adenomatous colon polyps. FAP is caused by germline *APC* mutations that are inherited in an autosomal dominant pattern, although *de novo* mutations occur in about 25% of cases. Adenomas in classic FAP are more numerous in the distal colon than in the proximal colon. Adenoma and cancer develop in 100% of classic FAP cases if surgery is not performed. The average age of colorectal cancer onset is 39 years, with a risk of 93% by age 50 years. An attenuated form of FAP (AFAP) causes fewer polyps (<100 synchronous polyps) with more proximal colonic distribution. The risk for colon cancer in patients with AFAP is about 70% by age 80 years, with an average age at onset of 58 years.

Both FAP and AFAP are associated with extracolonic intestinal manifestations (**Figure 26**). Duodenal adenomas require surveillance because the lifetime risk for duodenal adenocarcinoma is estimated at 4%. Fundic gland polyps of the stomach do not have malignant potential but can mask the presence of gastric adenomas and cancer; risk for gastric cancer is less than 1%. Patients are also at risk for desmoid tumors, especially after abdominal surgery, and for papillary thyroid cancer. Nonmalignant findings include extra teeth, sebaceous or epidermoid cysts, osteomas, and congenital hypertrophy of the retinal pigmented epithelium.

In classic FAP mutation carriers, screening with sigmoidoscopy or colonoscopy should begin at age 10 to 12 years and be repeated every 1 to 2 years. Screening in patients with AFAP can be delayed until age 20 to 25 years and should be performed with colonoscopy. For individuals with FAP and AFAP, screening with upper endoscopy should begin at age 25 to

TABLE 27. Hereditary Colorectal Cancer Syndromes

Syndrome	**Gene(s)**	**Gastrointestinal Manifestations**	**Other Features**	
			Malignant	**Benign and Other Features**
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Colon cancer Gastric cancer Small-bowel cancer Pancreatic cancer	Endometrial cancer Ovarian cancer Hepatobiliary cancer Urinary tract cancer Brain cancer Sebaceous skin adenoma/cancer	Microsatellite instability Proximal colon cancer Universal screening of all colon and endometrial cancers
FAP	*APC*	Colon cancer Gastric cancer Duodenal/ampullary adenomas Pancreatic cancer	>100 synchronous polyps Papillary thyroid cancer Brain/central nervous system	Genotype-phenotype correlation Fundic gland polyps of stomach Desmoid tumors Epidermal cysts Osteomas Congenital hypertrophy of retinal pigment epithelium
Attenuated FAP			<100 synchronous colon polyps	More proximal distribution
MutYH-associated polyposis	*MutYH*	Colon cancer Duodenal cancer	Similar to FAP	Autosomal recessive inheritance Monoallelic carriers have 1.5- to 2-fold increased colon cancer risk
Polymerase proofreading-associated polyposis	*POLE* *POLD1*	Oligo-adenomatous polyposis	Endometrial cancer	Possible microsatellite instability on tumor testing
Juvenile polyposis syndrome	*SMAD4* *BMPR1A*	Colon cancer Gastric cancer Small-bowel cancer Pancreatic cancer Juvenile polyps		Hereditary hemorrhagic telangiectasia Polyp complications: anemia, bleeding prolapse, pain, diarrhea, intussusception
Peutz-Jeghers syndrome	*STK11*	Small-bowel cancer Colon cancer Gastric cancer Pancreatic cancer Peutz-Jeghers-type polyps	Breast cancer Ovarian cancer (SCTAT) Uterine cancer Cervical cancer (adenoma malignum) Testicular cancer (Sertoli cell tumor) Lung cancer	Skin changes: mucocutaneous pigmentation on lips and buccal mucosa Symptoms of polyps: intussusception, ulceration, bleeding, infarction
PTEN hamartoma syndrome	*PTEN*	Colon cancer Gastric cancer Small bowel cancer Gastrointestinal hamartomatous polyps	Breast cancer Thyroid cancer Kidney cancer Endometrial cancer Skin (melanoma)	Large head circumference Characteristic benign skin findings
Serrated polyposis syndrome	Unknown	Colon cancer Serrated lesions	No current evidence for extra colonic surveillance	

FAP = familial adenomatous polyposis; SCTAT = sex cord tumor with annular tubules.

TABLE 28. Criteria for Lynch Syndrome

Amsterdam II Criteria	Revised Bethesda Criteria[a]
≥3 relatives with Lynch-related tumor	CRC diagnosed at age <50 years
≥2 generations affected	Synchronous, metachronous Lynch-related tumors independent of age
1 cancer diagnosed at age < 50 years	CRC with MSI-high-like histologic features[b] at age <60 years
1 relative a first-degree relative of the other two	CRC diagnosed in individual with ≥1 first-degree relative with Lynch-related tumor, if one was diagnosed at age <50 years
Familial adenomatous polyposis excluded	CRC diagnosed in individual with ≥2 first- or second-degree relatives with Lynch-related tumor, independent of age
Tumors confirmed by pathologic evaluation	

Lynch-related tumors include colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, biliary tract, brain, and small bowel cancer. Also included are sebaceous gland adenomas and keratocanthomas in Muir-Torre syndrome.

CRC = colorectal cancer; MSI = microsatellite instability.

[a] Tumors should be tested for MSI, or genetic testing may be considered if criteria are met.

[b] MSI-high-like histologic features include presence of tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous or signet-ring differentiation, and medullary growth pattern.

30 years and include visualization of the papilla with a duodenoscope. Fundic gland polyps in the stomach should be randomly sampled. Surveillance of the upper gastrointestinal tract is determined by duodenal findings. Annual thyroid ultrasonography is also recommended.

Colectomy is the treatment of choice for classic FAP and may be pursued in patients with AFAP. Absolute indications for surgery include cancer and significant symptoms, such as rectal bleeding. Relative indications include multiple adenomas greater than 6 mm; an increase in the number of polyps; adenoma with high-grade dysplasia; and multiple diminutive polyps, which can prevent identification of adenomas. The type of surgery depends on the polyp burden in the rectum. High rectal polyp burden typically necessitates total proctocolectomy with ileostomy or ileal anal pouch; otherwise, subtotal colectomy with ileorectal anastomoses may be possible. Postsurgical surveillance is yearly sigmoidoscopy for patients with an intact rectum and ileoscopy every 2 years for those with an ileostomy.

MutYH-Associated Polyposis

MutYH-associated polyposis (MAP) is an inherited syndrome characterized by fewer adenomas than classic FAP. MAP is caused by mutations in the *MutYH* gene, a component of base excision repair. In this recessive condition, affected patients inherited two mutated copies from their parents. Most patients have 20 to 99 adenomatous colon polyps. Some individuals can develop cancer with only a few or no synchronous adenomas. Mean age at cancer onset is about 52 years. In addition, patients with MAP can have other polyp types, including serrated lesions and hyperplastic polyps. Duodenal cancer risk in MAP is estimated at 4%, and surveillance with upper endoscopy is similar to that indicated in patients with FAP. Surgical management of the colon is also similar to that of FAP.

Other Adenomatous Polyposis Syndromes

Several recently described rare polyposis syndromes are inherited in an autosomal dominant manner. Polymerase proofreading-associated polyposis appears to have features of both FAP and Lynch syndrome and is caused by mutations in polymerase proofreading genes *POLE* and *POLD1*. Endometrial cancer has been described in this syndrome, and tumor testing shows microsatellite instability. Mutations in *GREM1* have also been associated with hereditary polyposis. Management

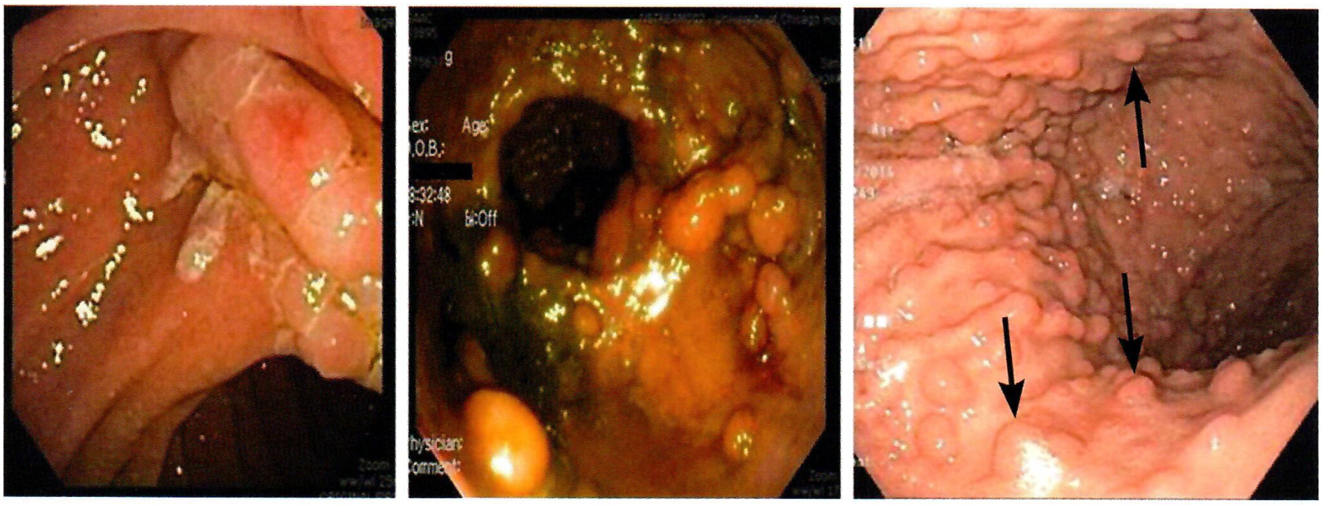

FIGURE 26. Intestinal features of familial adenomatous polyposis (FAP). Duodenal adenomas can also develop, especially involving the ampulla of Vater, and evolve into adenocarcinoma (*left*). If a patient with FAP has had surgery and has an ileorectal anastomosis, rectal polyps can develop in the remaining rectum (*center*). Numerous fundic gland polyps of the stomach can develop in FAP; these polyps have minimal malignant potential but can obscure the presence of gastric adenomas (*right, arrows*).

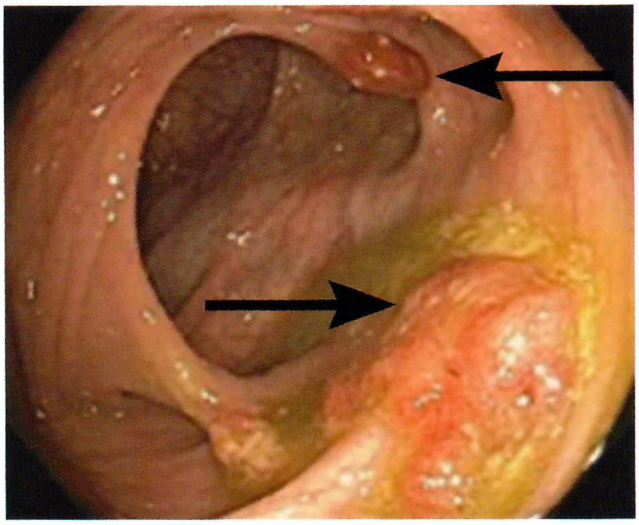

FIGURE 27. Endoscopic view of juvenile polyps (*arrows*) in the colon of a patient with juvenile polyposis syndrome. Juvenile polyps can have an erythematous and waxy appearance.

guidelines are not established, but management of colonic polyps follows similar principles as for other adenomatous polyp syndromes.

Hamartomatous Polyposis Syndromes

Hamartomas are polyps caused by overgrowth of normal tissue. Three primary syndromes are associated with hamartomas in the gastrointestinal tract: juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), and *PTEN* hamartoma syndrome (also known as Cowden syndrome).

JPS is caused by mutations in the *BMPR1A* and *SMAD4* genes. Its incidence is approximately 1 in 130,000 live births. Multiple juvenile polyps (>5 polyps) are found in the colon (98%), stomach (14%), and small bowel (14%) of patients with JPS (**Figure 27**). Sporadic juvenile polyps can be found in up to 1% of children and are not considered syndromic. The average age at JPS diagnosis is 18.5 years, and rectal bleeding is the most common symptom.

PJS is caused by mutations in the *STK11 (LKB1)* gene. Its incidence is approximately 1 in 200,000 live births. PJS hamartomas are found primarily in the small bowel but can also develop in the stomach and colon (**Figure 28**). PJS is also characterized by hyperpigmented mucocutaneous macules on the lips and buccal mucosa (**Figure 29**). Small-bowel hamartomas develop at a young age in patients with PJS and may present with intussusception, obstruction, and bleeding.

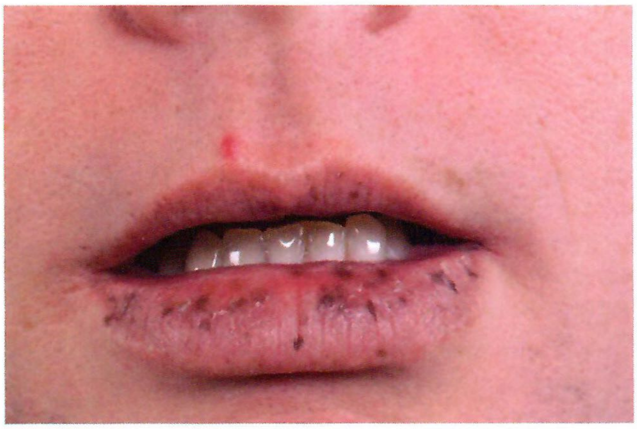

FIGURE 29. Peutz-Jeghers syndrome is associated with distinctive mucocutaneous pigmentations. The pigmented lesions occur most commonly on the lips and perioral region but can also occur on the nose, perianal area, and genitals.

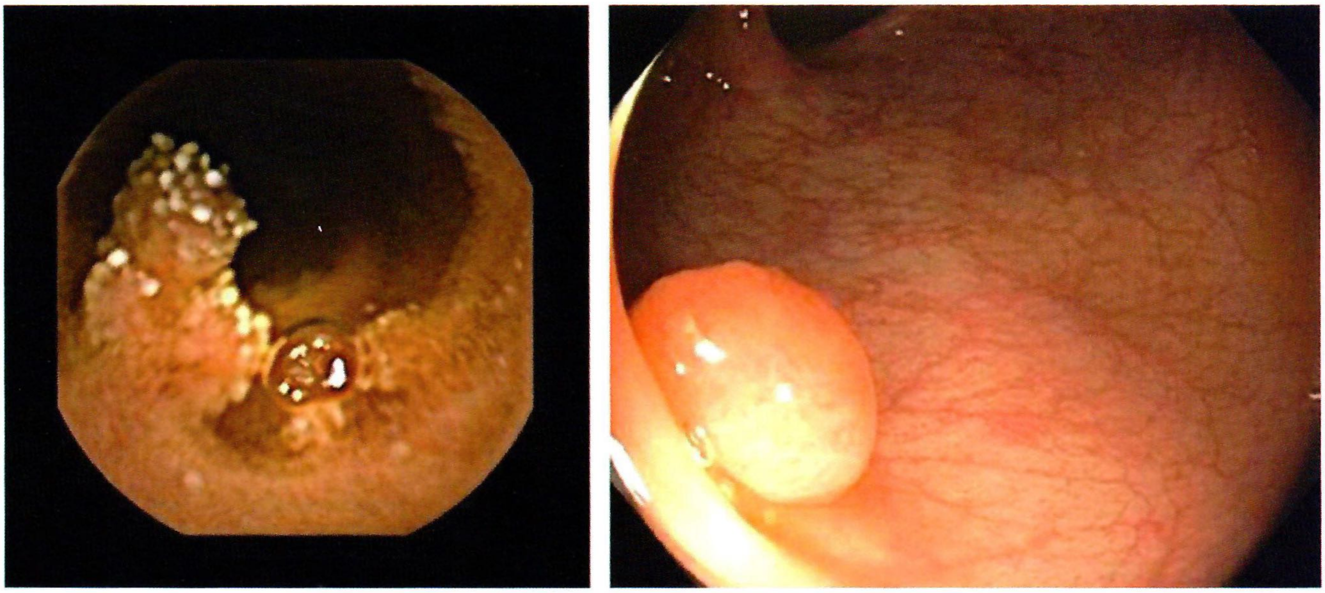

FIGURE 28. Peutz-Jeghers syndrome (PJS) polyps. Capsule endoscopy showing a PJS hamartomatous polyp in the small intestine (*left*); polyps in the small intestine can cause bleeding and/or obstructions. Colonoscopy showing a hamartomatous polyp in the colon of a patient with PJS (*right*).

PTEN hamartoma syndrome is caused by germline mutations in the tumor suppressor gene *PTEN*. Macrocephaly and characteristic benign skin findings are common, including facial trichilemmomas, lipomas, and oral papillomas.

Serrated Polyposis Syndrome

Serrated polyposis syndrome is characterized by numerous serrated polyps in the colon and an increased risk for colon cancer. The definition is based on having either of the following over the patient's lifetime:

- Five or more serrated polyps proximal to the rectum, all at least 5 mm and with two or more at least 10 mm
- More than 20 serrated polyps throughout the colon, at least five located proximal to the rectum

Estimates suggest that the prevalence of serrated polyposis syndrome is 0.3% to 0.6%. The genetic basis of the syndrome is unknown, although smoking appears to be a risk factor. Colonoscopy is recommended every 1 to 3 years with removal of all polyps greater than 5 mm. Surgery may be considered if the polyps cannot be managed endoscopically. No extracolonic manifestations have been noted in serrated polyposis syndrome.

KEY POINTS

- Lynch syndrome is caused by germline mutations in the mismatch repair genes and carries a lifetime risk for colorectal cancer of 50% to 80%.
- Lynch syndrome should be suspected in patients with synchronous or metachronous colorectal cancers, colorectal cancer before 50 years of age, occurrence of multiple Lynch syndrome–associated cancers, or family history of multiple cancers associated with Lynch syndrome.
- Colectomy is the treatment of choice for classic familial adenomatous polyposis and may be pursued in patients with the attenuated form of the disease.

Disorders of the Liver

Approach to the Patient With Abnormal Liver Chemistry Studies

Results of liver chemistry tests are frequently abnormal, and it is important to take a systematic approach to their evaluation. In general, liver test abnormalities can be used to categorize liver disease into hepatocellular or cholestatic patterns.

Elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels represent a hepatocellular pattern, reflecting hepatic parenchymal inflammation (hepatitis). Elevated ALT levels are more specific for hepatic inflammation because AST is also found in other tissues, such as heart and muscle. In patients with elevated aminotransferase levels, an AST-to-ALT ratio greater than 1 can suggest advanced liver disease as a result of decreased hepatic synthesis of ALT.

Elevations in alkaline phosphatase (ALP) and bilirubin levels represent a cholestatic pattern and typically result from biliary tree abnormalities. ALP is also produced in bone, red blood cells, and placenta, and high levels occur in pregnancy. ALP fractionation can determine the source of elevation.

Bilirubin has unconjugated and conjugated forms. Unconjugated hyperbilirubinemia often results from increased heme turnover in hematologic disease or benign alterations of bilirubin conjugation, such as Gilbert syndrome. Conjugated hyperbilirubinemia usually reflects a liver disorder.

Prothrombin time and serum albumin levels may reflect liver synthetic function, but other causes of abnormalities are also common. Albumin levels can be decreased in malnutrition, the nephrotic syndrome, acute inflammation, and protein-losing enteropathies. Prothrombin time can be prolonged in vitamin K deficiency, warfarin therapy, inherited or acquired factor deficiency, and the antiphospholipid antibody syndrome. The relative levels and severity of AST, ALT, and ALP elevations provide clues about the cause of liver disease (**Table 29**). The duration of abnormal liver test results is also important in evaluating causes of liver injury (acute liver inflammation: <6 months' duration; chronic hepatitis: ≥6 months' duration).

Abdominal imaging can be helpful in evaluating abnormal liver test results. Abdominal ultrasonography is an appropriate initial modality and may show increased echogenicity, consistent with fatty infiltration of the liver, as well as liver nodularity in patients with cirrhosis. Cross-sectional imaging, including CT and MRI, may show fatty infiltration of the liver, changes of cirrhosis, or sequelae of portal hypertension.

When fibrosis and cirrhosis are suspected, both serologic and imaging techniques are increasingly used to detect and estimate the extent of fibrosis and potentially avoid biopsy. The AST-to-platelet ratio and several proprietary serologic tests may provide valuable information on the degree of underlying fibrosis. Elastography is a noninvasive imaging technique (including ultrasonography, MRI, and transient elastography) that assesses liver stiffness as a measure of fibrosis. High stiffness values may also occur with hepatic congestion, infiltrative disorders, and bile duct obstruction.

KEY POINTS

- Elevated aspartate aminotransferase and alanine aminotransferase levels represent hepatic parenchymal inflammation; alanine aminotransferase levels are more specific for hepatic inflammation.
- Elevations in alkaline phosphatase and bilirubin levels represent a cholestatic pattern and may result from biliary abnormalities.
- Prothrombin time and serum albumin levels reflect liver synthetic function.
- Elastography is a noninvasive imaging technique that assesses liver stiffness as a measure of fibrosis and may avoid biopsy. **HVC**

TABLE 29. Typical Liver Chemistry Studies in Common Hepatobiliary Disorders

Disease	AST	ALT	ALP	Bilirubin	Other Features
Acute viral hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑↑	Exposure history, fatigue, nausea
Chronic viral hepatitis	↑	↑↑	Normal to ↑	Normal	History of exposure to infected blood or body fluids
Nonalcoholic steatohepatitis	Normal to ↑	Normal to ↑	Normal to ↑	Normal	Metabolic syndrome
Alcoholic hepatitis	↑↑	Normal to ↑	↑	Normal to ↑↑↑	Excess alcohol intake
Acute autoimmune hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑	Autoantibodies
Chronic autoimmune hepatitis	↑	↑↑	Normal to ↑	Normal	Autoantibodies
Wilson disease	↑	↑	Low	↑ and often unconjugated	Hemolysis if acute, neurologic symptoms if chronic
α_1-Antitrypsin deficiency	↑	↑	Normal	Normal	May have pulmonary disease
Hemochromatosis	Normal	Normal	Normal	Normal	Joint symptoms, family history, other organ involvement
Primary biliary cholangitis	↑	↑	↑↑↑	Normal	Female, sicca symptoms, antimitochondrial antibody
Primary sclerosing cholangitis	↑	↑	↑↑↑	Normal	Ulcerative colitis, abnormal cholangiogram
Large-duct obstruction	↑ (↑↑ if acute)	↑ (↑↑ if acute)	↑↑	↑↑	Pain if acute, dilated ducts on imaging
Infiltrative liver disease	↑	↑	↑↑↑	Normal	Features of malignancy, sarcoid, amyloid, or infection (fungal or mycobacterial)
Hepatic ischemia	↑↑↑	↑↑↑	Normal	Normal	AST >5000 U/L, history of hypotension
Celiac disease	Normal to ↑	Normal to ↑	Normal to ↑	Normal	Usually other features of celiac disease
Congestive hepatopathy	Normal to ↑	Normal to ↑	Normal to ↑	↑ to ↑↑↑	Cardiac disease, elevated jugular venous pressure

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Viral Hepatitis

Hepatitis A

Hepatitis A virus (HAV) is an RNA virus causing acute hepatitis mediated by the host immune response. HAV infection is usually self-limited, but atypical forms include relapsing-remitting infection with cholestatic features and, rarely, acute liver failure. HAV transmission is fecal-oral. Risk factors include international travel, contacts with HAV-infected household members, men who have sex with men, homelessness, and exposure to day care or institutionalized settings. HAV incidence declined dramatically after introduction of universal childhood HAV vaccination, but rates have recently increased among unvaccinated people, especially those reporting homelessness or drug use (see MKSAP 19 General Internal Medicine 2).

Mortality is rare but may be increased in patients with preexisting chronic liver disease. The incubation period for HAV is 15 to 50 days. A prodrome of malaise, nausea, vomiting, fever, and right-upper-quadrant pain is followed approximately 1 week later by jaundice and hepatomegaly. Laboratory studies may show aminotransferase levels exceeding 1000 U/L and total bilirubin level of 10 mg/dL (171 µmol/L) or higher, mostly direct (conjugated). Acute illness is diagnosed by HAV IgM antibodies, although false-positive results may occur within the setting of other viral infections. HAV IgG antibodies indicate previous infection or vaccination and provide immunity from reinfection. Treatment is supportive, and at least 90% of patients recover fully within 3 to 6 months of infection.

HAV can be transmitted during the prodrome stage and up to 1 week after development of jaundice. Persons who have recently been exposed to HAV and have not been immunized should receive postexposure prophylaxis as soon as possible (within 2 weeks of exposure). Postexposure prophylaxis should consist of HAV vaccine in all nonimmune persons age 12 months or older. Immunoglobulin administration may be considered in addition to vaccination in patients older than age 40 years because vaccine efficacy is uncertain in older patients. Immunoglobulin may also be administered to persons at high risk for complications, including those with chronic liver disease and immunosuppression.

TABLE 30. Indications for Hepatitis B Virus Testing[a]

Individuals born or raised in regions with high rates of hepatitis B virus infection, including Asia, Africa, the South Pacific, European Mediterranean countries, Eastern Europe, most of South America, Honduras, Guatemala, and the Middle East (except Israel and Cyprus)
U.S.-born persons not vaccinated as infants whose parents were born in endemic areas
Household or sexual contact with hepatitis B surface antigen–positive persons
Intravenous drug use
Multiple sex partners or history of sexually transmitted infection
Men who have sex with men
History of incarceration
History of hepatitis C virus
Persons with HIV infection
Persons undergoing predialysis, hemodialysis, peritoneal dialysis, or home dialysis
Persons with developmental disabilities and staff in residential facilities for persons with developmental disabilities
Pregnancy
Before initiation of immunosuppressive or cytotoxic therapy
Elevated aminotransferase levels of unknown cause

[a] Recommendations collated from the CDC, U.S. Preventive Services Task Force, and American Association for the Study of Liver Diseases.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus affecting 240 million persons worldwide. See MKSAP 19 General Internal Medicine 2 for HBV vaccination strategies. HBV can be transmitted perinatally; through sexual exposure, direct contact with blood, or percutaneous exposure; or by close person-to-person contact. The risk for chronic HBV infection decreases with increasing age at time of infection. Newborns acquiring HBV have the highest risk (90%), whereas adults have an approximately 5% risk. Screening for HBV infection with hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B antigens (anti-HBs and anti–hepatitis B core antigen [HBc]) is recommended in individuals with risk factors and before initiation of immunosuppressive or cytotoxic therapy (**Table 30**); anti-HBV prophylactic treatment should be considered in patients with chronic HBV infection. Interpretation of screening test results is listed in **Table 31**.

HBV infection presents as acute hepatitis in a minority of patients. Approximately 30% of adults may develop jaundice from acute infection, with aminotransferase levels as high as 3000 U/L and nonspecific symptoms (e.g., malaise, nausea, and right-upper-quadrant pain). Acute liver failure develops in approximately 0.5% of patients. Chronic HBV infection is diagnosed after 6 months in patients with persistent HBsAg detected in serum.

The four phases of chronic HBV infection are differentiated on the basis of immune response: immune tolerant,

TABLE 31. Interpretation of Hepatitis B Serology Test Results

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	HBV DNA (IU/mL)	ALT
Immunized	–	+	–	–	–	–	Normal
Acute infection	+	–	+ (IgM)	+	–	+	Increased
Resolved infection	–	+	+ (IgG)	–	+/–	–	Normal
Chronic HBV infection							
Immune tolerant chronic HBV infection	+	–	+ (IgG)	+	–	>1 million	Normal or mildly elevated
Immune active chronic HBV infection	+	–	+ (IgG)	+	–	>2000 HBeAg negative; >20,000 HBeAg positive	Increased (intermittent or persistent)
Inactive chronic HBV infection	+	–	+ (IgG)	–	+	<2000 (when measured every 3-4 months for 1 year)	Normal

ALT = alanine aminotransferase; Anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

Data from Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-99. [PMID: 29405329] doi:10.1002/hep.29800.

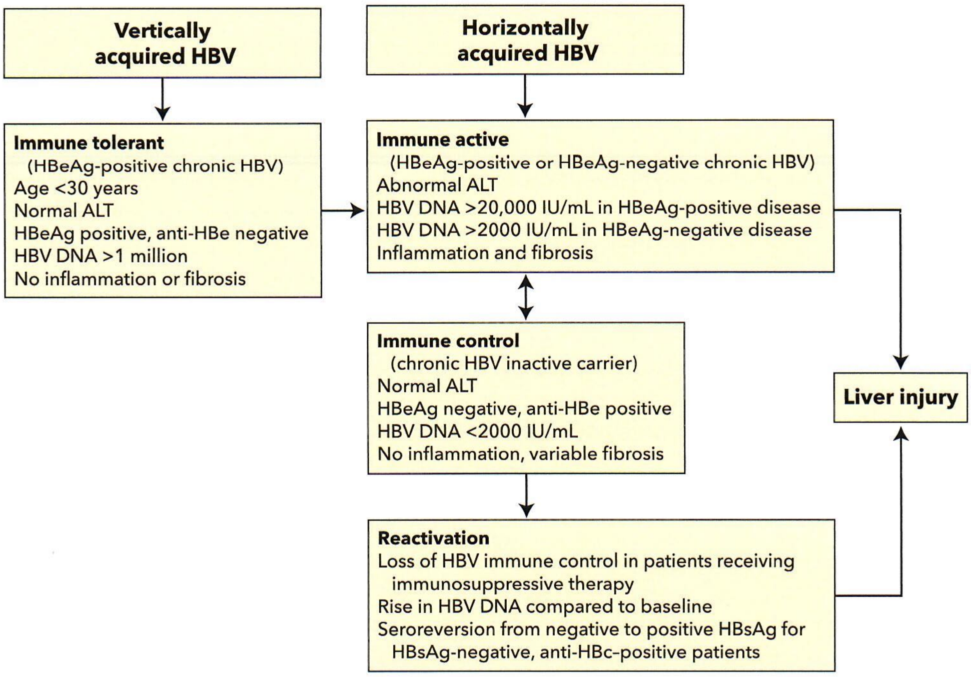
Vertically acquired HBV
Horizontally acquired HBV
Immune tolerant
(HBeAg-positive chronic HBV)
Age <30 years
Normal ALT
HBeAg positive, anti-HBe negative
HBV DNA >1 million
No inflammation or fibrosis
Immune active
(HBeAg-positive or HBeAg-negative chronic HBV)
Abnormal ALT
HBV DNA >20,000 IU/mL in HBeAg-positive disease
HBV DNA >2000 IU/mL in HBeAg-negative disease
Inflammation and fibrosis
Immune control
(chronic HBV inactive carrier)
Normal ALT
HBeAg negative, anti-HBe positive
HBV DNA <2000 IU/mL
No inflammation, variable fibrosis
Liver injury
Reactivation
Loss of HBV immune control in patients receiving immunosuppressive therapy
Rise in HBV DNA compared to baseline
Seroreversion from negative to positive HBsAg for HBsAg-negative, anti-HBc-positive patients

FIGURE 30. Phases of chronic hepatitis B virus infection. It is assumed that patients progress through the phases in sequence, although not all patients develop HBeAg-negative chronic hepatitis B, and only patients with vertical transmission of hepatitis B have a clinically recognized immune tolerant phase. All phases feature positivity for HBsAg, negativity for anti-HBs, and positivity for IgG anti-HBc.

ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBV DNA = hepatitis B virus DNA.

Data obtained from Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1570. PMID: 29405329 doi:10.1002/hep.29800.

immune active, immune control (inactive chronic HBV infection, which occurs at a rate of 10% per year in previously immune active patients), and reactivation.

Reactivation of chronic HBV infection results from loss of immune control in patients with HBsAg-positive/anti-HBc–positive disease or with HBsAg-negative/anti-HBc–positive disease. This often occurs in patients receiving immunosuppressive therapy. Reactivation is characterized by a rise in HBV DNA compared with baseline and seroconversion from HBsAg negativity to HBsAg positivity in HBsAg-negative/anti-HBc–positive patients. Reactivation may be asymptomatic, result in a hepatitis flare (evidenced by an ALT greater than 100 U/L and more than threefold above baseline), or result in hepatic failure (**Figure 30**).

Approximately 40% of deaths in HBV-infected persons older than 40 years are related to hepatocellular carcinoma or decompensated cirrhosis. Risk factors for these conditions in patients with chronic HBV infection are listed in **Table 32**; see Hepatocellular Carcinoma for recommendations on hepatocellular carcinoma screening and surveillance.

Treatment is advised for patients with acute liver failure, infection in the immune-active phase or reactivation phase, and cirrhosis as well as in selected immunosuppressed patients. First-line treatment is entecavir or tenofovir. Lamivudine, adefovir, and telbivudine are less commonly used because of resistance. Pegylated interferon can be used for 48 weeks in patients without cirrhosis who have high ALT levels and low HBV DNA levels.

Treatment goals for patients in the HBeAg-positive immune-active phase are HBeAg loss with anti-HBe seroconversion, which should then be followed by an additional 12 months of treatment. Goals of treatment in the HBeAg-negative immune-active phase are HBV DNA suppression and ALT normalization; oral antiviral agents are generally continued indefinitely in this setting. HBsAg seroconversion rarely occurs with oral antiviral treatment and therefore is not a treatment goal. Patients with cirrhosis should continue oral antiviral medications indefinitely.

TABLE 32. Risk Factors for Cirrhosis or Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Virus Infection

Age >40 years
Hepatitis B virus DNA level >2000 IU/mL
Elevated alanine aminotransferase level
Genotype C infection
Heavy alcohol use
Development of hepatitis B e antigen–negative reactivation phase of chronic hepatitis B virus infection
HIV infection
Hepatitis C virus or hepatitis D virus infection

Prophylactic oral antiviral therapy should be given to patients who are HBsAg-positive or isolated core antibody-positive and are receiving B-cell–depleting therapy (e.g., rituximab or ofatumumab), prednisone (≥10 mg/d for at least 4 weeks), or anthracycline derivatives. Patients receiving tumor necrosis factor-α or tyrosine kinase inhibitors should also be considered for prophylaxis.

Rarely, patients with HBV infection develop membranous nephropathy, membranoproliferative nephropathy, polyarteritis nodosa, or cryoglobulinemia, all of which should prompt oral antiviral therapy.

The survival rate after liver transplantation for end-stage liver disease from HBV infection is greater than 90% at 1 year. Recurrence of HBV infection in transplant recipients is prevented with HBV immunoglobulin and/or oral antiviral therapy.

Hepatitis C

Worldwide, approximately 150 million individuals are infected with hepatitis C virus (HCV). HCV is most commonly transmitted through intravenous or intranasal drug use, blood transfusions before 1992, or sexual intercourse, although the efficiency of viral spread through vaginal intercourse is low. All patients aged 18 to 79 years should be screened for HCV, followed by HCV RNA testing if those results are positive. Although guidelines from the U.S. Preventive Services Task Force suggest not screening patients older than 79 years in the absence of specific risk factors, the CDC does not specify an upper age limit. Other patients with risk factors may also require testing (**Table 33**). Patients with positive HCV antibody and RNA results have active infection and should undergo genotyping.

Acute HCV infection is usually asymptomatic, but jaundice, nausea, right-upper-quadrant pain, dark urine, and acholic stools can occur. Evaluation of suspected acute infection includes HCV antibody and RNA tests. The HCV RNA result becomes positive first, followed by HCV antibody within 12 weeks of infection. The antibody remains positive for life but does not confer immunity from reinfection. Spontaneous clearance (usually within 6 months) is more common in women, younger patients, and patients with symptoms, high ALT levels, or the *IL-28 CC* genotype. Monitoring HCV RNA levels for clearance at 3 and 6 months is recommended in patients with acute infection.

HCV results in chronic infection in 60% to 80% of patients; up to 30% progress to cirrhosis over two to three decades. Risk for hepatocellular carcinoma in patients with cirrhosis is 2% to 4% per year.

Several extrahepatic diseases are associated with chronic HCV infection, including non-Hodgkin lymphoma, membranoproliferative glomerulonephritis, and mixed cryoglobulinemia. Chronic HCV infection is also the most common cause of porphyria cutanea tarda, although it is also associated with alcohol-induced liver damage and hemochromatosis. It presents with increased skin fragility noted on sun-exposed areas, most frequently the dorsal hands. Small vesicles rupture, leaving erosions (**Figure 31**). Treatment of porphyria cutanea tarda is aimed at avoiding sun exposure

TABLE 33. Conditions Requiring Testing for Hepatitis C Virus

Age 18-79 years[a]
Injection-drug use or intranasal illicit-drug use (ever)
Long-term hemodialysis (ever)
Percutaneous/parenteral exposures in an unregulated setting (nonsterile technique)
Needlesticks, sharps, or mucosal exposure to hepatitis C virus–infected blood
Children born to women infected with hepatitis C virus
Receipt of blood or blood-components transfusion or organ transplantation before 1992
Receipt of clotting-factor concentrates produced before 1987
History of incarceration
HIV infection
Sexually active persons about to start pre-exposure prophylaxis for HIV
Undiagnosed chronic liver disease
Elevated alanine aminotransferase level
Living organ donors before donation

[a] This age range is recommended in guidelines from the U.S. Preventive Services Task Force. The CDC does not specify an upper age limit for screening.

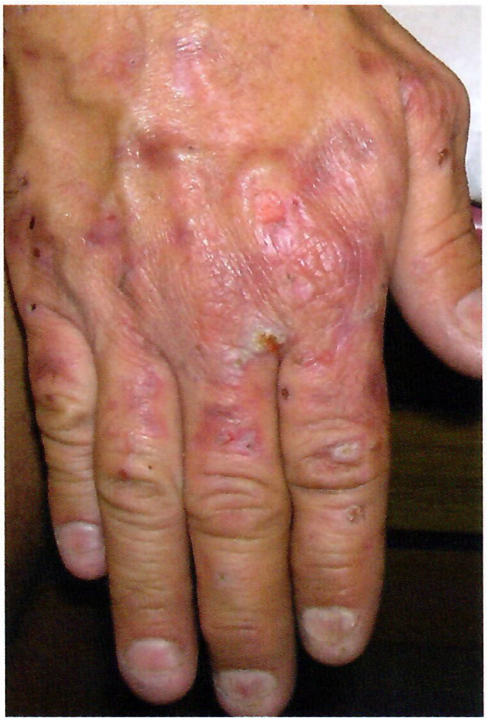

FIGURE 31. Porphyria cutanea tarda manifests as a chronic blistering disease with epidermal erosions on sun-exposed skin, especially on the backs of the hands.

and decreasing iron overload with phlebotomy; low-dose hydroxychloroquine is a second-line option.

All HCV-infected patients should be tested for HBV (see Hepatitis B section for further discussion) because of the potential shared routes of transmission. Susceptible patients should receive HBV vaccination. HBV can be reactivated during direct-acting antiviral therapy for HCV infection. Patients who test positive for HBsAg with detectable HBV DNA and who do not meet standard HBV treatment criteria should undergo HBV DNA monitoring approximately every 4 weeks until 12 weeks after completion of HCV treatment, or they can receive oral HBV therapy prophylactically.

All HCV-infected patients except those with a short life expectancy should be considered for treatment. Patients with decompensated cirrhosis should see a hepatologist before treatment and be considered for liver transplantation.

Patients being considered for treatment require a pretreatment fibrosis assessment (see Approach to the Patient With Abnormal Liver Chemistry Studies). Noninvasive assessment using fibrosis serologic biomarkers and/or elastography is preferred unless patients have a documented short duration of disease, decompensated cirrhosis, or a radiologic diagnosis of cirrhosis. Routine liver biopsy for pretreatment fibrosis assessment is not recommended.

Treatment regimens include a combination of direct-acting antivirals with the use of different mechanisms to prevent viral reproduction. Regimens are chosen based on genotype, treatment experience and response, and fibrosis status (current recommendations on HCV treatment regimens can be found at www.hcvguidelines.org). Patients are often managed by a hepatologist or infectious disease specialist because retreatment guided by resistance-associated substitution may be necessary.

Cure rates exceed 90% in most patients. Cure is defined by no HCV RNA in blood 12 weeks after treatment ends. HCV antibody positivity remains indefinitely and should not be rechecked. Patients can become reinfected after new exposures, and HCV RNA testing is appropriate to identify new infection. Virologic cure reduces risk for progression to cirrhosis, complications of cirrhosis, hepatocellular carcinoma, and liver-related mortality. Patients with advanced (METAVIR stage F3) fibrosis require ongoing surveillance for hepatocellular carcinoma even after virologic cure. Patients with cryoglobulinemic vasculitis and non-Hodgkin lymphoma are more likely to experience remission when HCV is eradicated.

Hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus that requires concurrent infection with HBV for human infection. HDV infection is endemic in the Mediterranean basin and Pacific islands and uncommon in Western countries. It is diagnosed through detection of HDV IgG. The clinical course ranges from inactive disease to acute hepatitis, with occasional progression to chronic liver disease (in the case of simultaneous HBV-HDV co-infection) and to fulminant hepatitis in HDV superinfection in a patient with previous HBV infection. HDV-infected patients with evidence of progressive liver disease should receive 12-month pegylated interferon treatment; cure rates are 25% to 45%.

Hepatitis E

Hepatitis E virus (HEV) is an RNA virus with worldwide distribution. There are four genotypes: Genotypes 1 and 2 are more common in developing countries and are transmitted by the fecal-oral route through contaminated water; genotypes 3 and 4 are more common in developed countries, where transmission occurs through contaminated food, mostly pork or venison. In developing countries, HEV infection generally occurs in young adults and can occur in large epidemics. In developed countries, HEV usually affects men older than 40 years. The incubation period is 2 to 5 weeks. Approximately 50% of cases are asymptomatic. Symptoms of HEV infection are jaundice, malaise, nausea, vomiting, anorexia, and right-upper-quadrant pain. Aminotransferase levels are usually elevated to 1000 to 3000 U/L. Diagnosis relies on detecting HEV IgM or RNA. Treatment is supportive, and recovery is expected in 4 to 6 weeks. Chronic HEV infection is typically seen only in immunocompromised patients. HEV infection should be considered in patients with an unknown cause of acute hepatitis and in immunocompromised patients with chronic hepatitis. Solid-organ transplant recipients with chronic HEV infection may require ribavirin treatment and have response rates of 70%.

Other Viruses

Other viruses can cause hepatitis. These viruses along with their symptoms, laboratory findings, and treatment options are listed in **Table 34**.

KEY POINTS

- Treatment of hepatitis A virus infection is supportive, and 90% of patients or more recover fully within 3 to 6 months of infection.
- Treatment of hepatitis B virus infection is advised for patients with acute liver failure, infection in the immune-active phase or the reactivation phase, and cirrhosis, and for immunosuppressed patients.
- All patients aged 18 to 79 years should be screened for HCV followed by HCV RNA testing if the results are positive.
- All hepatitis C virus–infected patients except those with a short life expectancy should be considered for treatment; cure rates exceed 90% in most patients.
- Hepatitis E virus infection should be considered in patients with an unknown cause of acute hepatitis and in immunocompromised patients with chronic hepatitis.

TABLE 34. Other Viral Causes of Hepatitis[a]

Infection	Symptoms/Laboratory Findings	Diagnosis	Treatment/Outcome
Cytomegalovirus	Mimics EBV-related mononucleosis Mild aminotransferase elevations	CMV serologies in immunocompetent host	Supportive; spontaneous recovery is norm
Primary herpes simplex virus in women in third trimester of pregnancy	Fever, altered mental status, right-upper-quadrant pain, hepatomegaly, presentation similar to sepsis Aminotransferase levels ≥5000 U/L, disproportionately low bilirubin level, coagulopathy	PCR; herpes simplex virus testing; liver biopsy showing intranuclear inclusions, multinucleated giant cells, and coagulative necrosis with minimal inflammation	IV acyclovir; 80% case-fatality rate in untreated patients
Primary varicella zoster virus (rare)	Primary infection in organ transplant recipients can cause acute liver failure	Biopsy of skin or affected organ	IV acyclovir
Parvovirus B19	Fever, rash, arthralgias Transiently elevated aminotransferase levels	Serologic tests demonstrating positivity for parvovirus B19-specific IgM antibody	Supportive; rarely associated with fulminant hepatic failure

CMV = cytomegalovirus; EBV = Epstein-Barr virus; IV = intravenous; PCR = polymerase chain reaction.

[a]Other viruses associated with elevated liver chemistries: human herpes virus 6, 7, and 8 and adenoviruses.

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic inflammatory hepatitis that is four times more common in women than men and can be associated with other autoimmune diseases (autoimmune thyroiditis, rheumatoid arthritis, or ulcerative colitis). It can affect individuals at any age but most frequently occurs in middle-aged adults. Presentation of autoimmune hepatitis varies from asymptomatic elevation of aminotransferase levels to extrahepatic symptoms, such as myalgia and malaise, to acute liver failure. Diagnosis is based on laboratory results (including positivity for antinuclear and smooth-muscle antibodies and elevated IgG levels), exclusion of other diagnoses (e.g., Wilson disease, viral hepatitis, and drug-induced liver injury), and liver histology.

Treatment includes a combination of prednisone and azathioprine for most patients. Prednisone monotherapy may be less preferable because of adverse effects, although azathioprine requires monitoring for cytopenia and may cause drug-induced hepatitis. Biochemical response occurs in 3 to 8 months for the 85% of patients whose disease responds to standard treatment, but histologic response can lag by many months. Duration of treatment should be 2 to 3 years before consideration of withdrawal. Liver biopsy is recommended to determine histologic response before consideration of drug withdrawal. High relapse rates after discontinuation of treatment underscore the need for serial monitoring of liver tests. Patients with severe acute autoimmune hepatitis presenting with jaundice should be managed by a hepatologist, and patients with features of acute liver failure require urgent transfer to a transplant center.

KEY POINTS

- Diagnosis of autoimmune hepatitis is based on elevated aminotransferase levels, positivity for antinuclear antibody and smooth-muscle antibody, elevated levels of IgG, and liver histology.
- Treatment of autoimmune hepatitis includes a combination of prednisone and azathioprine for most patients; duration of treatment should be 2 to 3 years before consideration of withdrawal.

Alcohol-Induced Liver Disease

Alcohol injury to the liver may take the form of steatosis, steatohepatitis, fibrosis, or cirrhosis. A history of alcohol use is the most important component in making the diagnosis, although not all patients are forthcoming about alcohol use. See MKSAP 19 General Internal Medicine 2 for more information about screening for alcohol use disorder. Most patients with alcoholic liver disease have consumed more than 100 g of alcohol daily for 20 years. Alcoholic hepatitis is a distinct clinical syndrome of severe steatohepatitis on a background of chronic alcoholic liver disease, often presenting with fever, jaundice, tender hepatomegaly, and leukocytosis. Approximately 25% of heavy drinkers develop cirrhosis. Differentiating alcoholic hepatitis from decompensated cirrhosis in patients with underlying cirrhosis can be difficult.

Physical examination may show evidence of hepatomegaly in patients with steatosis or steatohepatitis. In patients with alcoholic hepatitis or cirrhosis, findings of advanced liver disease may be present, including muscle wasting, scleral icterus, jaundice (including sublingual jaundice), spider angiomata, gynecomastia, testicular atrophy, or palmar erythema. Laboratory evaluation of alcohol-induced liver disease may show an elevated mean corpuscular volume, AST-to-ALT ratio greater than 2, elevated γ-glutamyl transferase level, elevated phosphatidyl ethanol level, and, in advanced cases, elevated INR and thrombocytopenia. The IgA level may be elevated. The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease-nonalcoholic-fatty-liver-disease-index) can help distinguish alcoholic liver disease from nonalcoholic fatty liver disease. The predictive model is based on AST, ALT, mean corpuscular volume, age, height, weight, and sex.

Alcoholic hepatitis is most often diagnosed clinically, with liver biopsy reserved for diagnostic uncertainty. Severity of alcoholic hepatitis can be determined by the Maddrey discriminant function (MDF) score, which is calculated as follows:

$$\begin{aligned}\text{MDF score} = 4.6\ &(\text{prothrombin time [s]}\\ &- \text{control prothrombin time [s]})\\ &+ \text{total bilirubin (mg/dL)}\end{aligned}$$

The Model for End-Stage Liver Disease (MELD) score (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/) can also be used to assess severity, with a MELD score greater than 20 suggesting moderate to severe disease. (See Classification of Liver Disease Severity for additional details on components of this score.)

In severe cases (MDF score ≥32, MELD score >20, or hepatic encephalopathy), treatment with prednisolone (which does not require hepatic metabolism, unlike prednisone) is recommended. Contraindications to prednisolone include active infection, upper gastrointestinal bleeding, acute kidney injury, concomitant liver disease (especially HCV and HBV), and multiorgan failure. The STOPAH trial showed a trend toward improvement in 28-day mortality with prednisolone, but results were not statistically significant. However, a meta-analysis of randomized studies (including STOPAH) showed that glucocorticoids reduced short-term mortality by 46%. Pentoxifylline is no longer recommended for treatment of alcoholic hepatitis and is not effective in patients whose symptoms do not respond to prednisolone.

Response to glucocorticoids can be assessed on day 7 with the Lille score (www.mdcalc.com/lille-model-alcoholic-hepatitis). Because of risk for infection, prednisolone should be discontinued in patients with no response (Lille score ≥0.45). A Lille scores below 0.45 supports prednisolone continuation for 28 days.

Nonsevere alcoholic hepatitis (MDF score <32; MELD score ≤20) requires supportive measures and should not be treated with prednisolone. All patients require assessment for nutritional deficiencies, nutritional management, thiamine replacement, and alcohol treatment, with a goal of abstinence.

Alcoholic cirrhosis can be diagnosed on clinical and radiologic grounds in patients with obvious evidence of portal hypertension and a history of consistent alcohol intake. Liver biopsy is sometimes necessary in cases with diagnostic ambiguity. In patients who drink alcohol, liver inflammation increases stiffness, making elastography inaccurate. Nutritional assessments and alcohol treatment are required. Alcohol abstinence can result in significant stabilization of liver function and reversal of portal hypertension. Patients with alcoholic liver disease and evidence of cirrhosis with or without portal hypertension should be referred to hepatology for further management and consideration of liver transplantation, regardless of duration of alcohol abstinence. Alcohol-induced liver disease is the second most common reason for liver transplantation in the United States, behind HCV.

KEY POINTS

- The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index can help distinguish alcoholic liver disease from nonalcoholic fatty liver disease.
- Manifestations of alcoholic hepatitis include fever, jaundice, tender hepatomegaly, and leukocytosis.
- Severity of alcoholic hepatitis is determined by the Maddrey discriminant function (MDF) score and Modified End Stage Liver Disease (MELD) score; patients with an MDF score of 32 or greater, MELD score greater than 20, or hepatic encephalopathy may be considered for prednisolone therapy.
- Pentoxifylline is no longer recommended for treatment of alcoholic hepatitis.
- All patients with advanced alcoholic liver disease should be referred to hepatology for further management and consideration of liver transplantation, regardless of duration of alcohol abstinence.

Drug-Induced Liver Injury

Drug-induced liver injury encompasses a spectrum of liver injury and can be induced by prescription, over-the-counter, and herbal medications. Patients should be asked about exposure to medications in the past 6 months, both prescription and nonprescription, including supplements. Use of the National Institute of Health's Web-based tool LiverTox (www.livertox.nih.gov) can help assess risk for hepatotoxicity.

Acetaminophen is the medication most recognized to have intrinsic hepatotoxicity. People who chronically drink alcohol can develop acetaminophen hepatotoxicity even when taking therapeutic doses of acetaminophen. The early recognition of acetaminophen-induced liver injury is critical so that *N*-acetylcysteine can be administered promptly to prevent liver failure.

Antibiotics (particularly amoxicillin-clavulanate) and antiepileptics (phenytoin and valproate) are also commonly associated with drug-induced liver injury, representing 60% of cases. Other than acetaminophen, the drugs most often causing acute liver failure in the United States are antituberculosis drugs, sulfa-containing antimicrobial agents, and antifungal agents.

The pattern of liver test abnormalities and histologic injury can be unpredictable. In addition to the hepatocellular pattern seen with acetaminophen, a cholestatic pattern (e.g., with amoxicillin-clavulanate) or mixed picture (e.g., with phenytoin) may be present. Liver injury typically resolves after discontinuation of the offending drug; resolution of liver injury supports the diagnosis. Re-exposure to the drug to demonstrate recurrence is not advisable because of risk for severe toxicity upon rechallenge.

Jaundice that occurs with cholestatic drug reactions can take months to resolve. A bilirubin level twice the upper limit of normal with ALT levels greater than three times the upper limit of normal is associated with mortality rates as high as 14%. Until resolution occurs, progression to liver failure and a need for liver transplantation are possible.

KEY POINTS

- Acetaminophen, antibiotics (particularly amoxicillin-clavulanate), and antiepileptics (phenytoin and valproate) are the most common causes of drug-induced liver injury.
- Liver injury typically resolves after discontinuation of the offending drug; resolution of liver injury supports the diagnosis.

Acute Liver Failure

Acute liver failure is the onset of hepatic encephalopathy and prolonged coagulation within 26 weeks of jaundice or other symptoms of liver inflammation in the absence of chronic liver disease. The most common cause of acute liver failure in the United States is acetaminophen overdose. Other widely recognized causes are presented in **Table 35**. Diagnosis requires immediate referral to a liver transplant center.

TABLE 35. Causes of Acute Liver Failure
Acetaminophen
Other medications (e.g., antituberculosis drugs, sulfa-containing antimicrobial agents, antifungal agents, herbal supplements, MDMA)
Hepatitis A virus
Hepatitis B virus (with or without hepatitis D virus)
Hepatitis E
Herpes simplex virus, cytomegalovirus, varicella zoster virus, Epstein-Barr virus
Autoimmune hepatitis
Wilson disease
Acute hepatic ischemia (e.g., systemic hypotension, Budd-Chiari Syndrome)
Amanita phalloides mushrooms
Acute fatty liver of pregnancy

MDMA = 3,4-methylenedioxy-methamphetamine.

Patients with acute liver failure require careful monitoring of mental status because progressive hepatic encephalopathy can result in cerebral edema (see Hepatic Encephalopathy). Kidney injury is common, and continuous renal replacement therapy is better tolerated than intermittent hemodialysis. Patients with acute liver failure are at risk for hypoglycemia and infection.

Specific treatment is based on the cause, and prompt treatment is crucial. For example, mortality rates for acetaminophen intoxication are lowest when *N*-acetylcysteine is administered within 12 hours of ingestion.

KEY POINTS

- The most common cause of acute liver failure in the United States is acetaminophen overdose.
- Diagnosis of acute liver failure requires immediate referral to a liver transplant center.

Metabolic Liver Diseases

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the world. Some 30% of the U.S. population may have this condition. Most patients with NAFLD do not have liver inflammation, and fat in the liver without inflammation or fibrosis is considered a relatively benign condition. Five percent to 12% of the U.S. population has fatty liver with inflammation (nonalcoholic steatohepatitis [NASH]) and may have progressive disease that can lead to fibrosis and cirrhosis. Unrecognized NASH is likely a major cause of cryptogenic cirrhosis.

NAFLD is a component of the metabolic syndrome. Consequently, the American Diabetes Association recommends that patients with type 2 diabetes or prediabetes and elevated ALT levels or fatty liver on ultrasonography should be evaluated for NASH and liver fibrosis. The mechanisms by which patients with NAFLD develop NASH are not fully understood, but metabolic, genetic, and environmental factors play a role.

NAFLD symptoms are nonspecific and may include fatigue and vague right-upper-quadrant abdominal pain. Mildly elevated hepatic aminotransferase levels are common in NASH but can be normal even with advanced fibrosis. NAFLD is often diagnosed by the presence of hepatic fat on ultrasonography, CT, and MRI.

Besides liver biopsy, no tests can diagnose NASH as a cause of chronically elevated liver chemistries. Patients with elevated liver chemistries, a negative serologic evaluation for alternative causes, clinical features of the metabolic syndrome, and characteristic abdominal imaging are presumed to have NAFLD. High autoantibody titers (antinuclear antibody, anti-smooth muscle antibody) are present in 20% of patients with NAFLD, but the clinical significance of this is unknown. The NAFLD fibrosis score (www.nafldscore.com) uses clinical data to identify patients at risk for severe disease. Transient elastography can help determine whether patients with NASH have developed significant hepatic fibrosis. Liver biopsy is indicated when the diagnosis is in doubt or the presence of hepatic fibrosis cannot otherwise be determined.

NAFLD management focuses on weight loss through diet and lifestyle modification. No specific diet for NAFLD is recommended, although carbohydrate-restricted diets may result in greater reduction in liver fat compared with other diets. Bariatric surgery and concomitant weight loss exceeding 8% to 10% improve NAFLD-associated inflammation and fibrosis. No drugs are FDA-approved for primary treatment of NAFLD. Cardiovascular disease is the leading cause of death in patients with NASH, and statin therapy should be considered, even in the presence of elevated aminotransferase levels.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is an autosomal co-dominant genetic disorder that results in accumulation of a variant form of α_1-antitrypsin in the liver. Homozygosity for this condition may cause liver injury and eventual cirrhosis. The hepatic accumulation of α_1-antitrypsin also decreases circulating α_1-antitrypsin, leading to lack of inhibition of elastase and resultant lung disease. Patients heterozygous for α_1-antitrypsin deficiency are at increased risk for liver injury in the setting of other liver diseases, including viral hepatitis and fatty liver disease. Supplemental α_1-antitrypsin prevents progressive lung injury but does not affect cirrhosis progression. Liver transplantation is required to treat liver failure resulting from α_1-antitrypsin deficiency.

Hereditary Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive condition characterized by excessive accumulation of iron in the liver due to a mutation in the genes that control hepcidin synthesis, resulting in increased iron absorption. It typically results from homozygosity of the C282Y polymorphism of the *HFE* gene, but other polymorphisms, such as H63D, can also cause disease. Cirrhosis can develop in untreated patients with hereditary hemochromatosis and is associated with an increased risk for hepatocellular carcinoma.

Elevated transferrin saturation and elevated serum ferritin levels suggest hereditary hemochromatosis, but genetic testing is required to confirm the diagnosis.

Cirrhosis should be suspected in all patients with hereditary hemochromatosis who have a serum ferritin level greater than 1000 ng/mL (1000 µg/L) or those with physical examination or imaging findings suggesting cirrhosis. Removal of excessive iron, usually by phlebotomy, prevents cirrhosis. Patients with cirrhosis should undergo iron-lowering therapy to stabilize liver disease and prevent other organ manifestations of iron overload; they should also be screened for hepatocellular carcinoma. Liver failure from hereditary hemochromatosis is treated by liver transplantation.

First-degree relatives of patients with hereditary hemochromatosis should be screened with iron studies, including transferrin saturation and serum ferritin level with *HFE* genotype testing if results of iron studies are abnormal. Children of affected patients can be reassured that they do not have hemochromatosis if the other parent has a normal *HFE* genotype.

Hemochromatosis is discussed further in MKSAP 19 Hematology.

Wilson Disease

Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive disorder that causes copper accumulation in the liver. Copper accumulation can result in a range of clinical presentations, including asymptomatic liver enzyme abnormalities, cirrhosis, and acute liver failure. Acute liver failure in Wilson disease may be accompanied by Coombs-negative hemolytic anemia (secondary to sudden release of copper from hepatocytes) and acute kidney injury. Unexplained liver disease or liver failure in any patient younger than age 40 years should prompt an investigation for Wilson disease, although older patients with Wilson disease have also been described.

Neurologic and behavioral changes can be seen in patients with Wilson disease (tremor, early-onset Parkinson disease, dystonia). Kayser-Fleischer rings can be seen on slit-lamp examination in nearly all patients with Wilson disease and neurologic findings and in 50% of patients with liver manifestations. Laboratory findings include high levels of urinary copper and low levels of ceruloplasmin and ALP. Histologic changes on liver biopsy can be nonspecific, although hepatic copper levels are typically high. Genetic testing for *ATP7B* gene mutations confirms Wilson disease.

Treatment is lifelong and involves administration of copper chelators. Trientine is preferred over penicillamine because of a lower rate of adverse effects. Zinc supplements can be administered to decrease intestinal absorption of copper. Urgent liver transplantation is necessary in acute liver failure secondary to Wilson disease.

KEY POINTS

- Nonalcoholic fatty liver disease is the most common cause of liver disease in the world, and management is focused on weight loss through dietary and lifestyle modification.
- α_1-Antitrypsin deficiency is an autosomal co-dominant genetic disorder that results in accumulation of a variant protein in the liver; homozygosity can result in liver injury and cirrhosis.
- Hereditary hemochromatosis is characterized by excessive iron absorption that results in accumulation of iron in the liver and cirrhosis.
- Wilson disease is a rare autosomal recessive disorder that causes accumulation of copper in the liver; it can present in young patients (<40 years) with acute liver failure accompanied by Coombs-negative hemolytic anemia and acute kidney injury.

Cholestatic Liver Disease

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), previously termed primary biliary cirrhosis, is an autoimmune disease affecting the small and medium bile ducts. The female-to-male predominance is 9 to 1. PBC is often asymptomatic but can present with fatigue and pruritus. Liver chemistry tests usually demonstrate a cholestatic pattern of injury, and the alkaline phosphatase may be significantly elevated. Diagnosis of PBC does not require liver biopsy when the ALP level is at least 1.5 times the upper limit of normal and antimitochondrial antibody results are positive or, if results are negative, other PBC-specific autoantibodies, including sp100 or gp210, are present. In patients with negative antibody results and strong suspicion for PBC, liver biopsy is necessary. Elastography can be used for fibrosis staging.

Initial treatment is ursodeoxycholic acid, which results in histologic improvement, improves survival rates, and diminishes the need for liver transplantation. Response to treatment is defined by improvement of the ALP level to less than 1.67 times the upper limit of normal. Patients who present with normal bilirubin and albumin levels and respond to treatment have a life expectancy similar to that of individuals without PBC. Patients whose disease does not respond to ursodeoxycholic acid should receive fibrates (off label) or obeticholic acid.

PBC is associated with other autoimmune conditions, particularly autoimmune thyroid disease. Thus, thyroid-stimulating hormone level should be checked yearly. In patients with cirrhosis and a PBC score of 4.1 or greater (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/updated-natural-history-model-for-primary-biliary-cirrhosis) or transient elastography results of 17 kPa or greater, upper endoscopy is indicated to assess for esophageal varices.

Patients with advanced disease should be managed like other patients with cirrhosis and portal hypertension (see Complications of Advanced Liver Disease). In addition, men with PBC and all patients with PBC and cirrhosis should be screened for hepatocellular carcinoma (see Hepatocellular Carcinoma for recommendations on screening and surveillance). Patients with PBC have increased risk for osteoporosis and should ensure daily intake of 1000 to 1500 mg of calcium and 1000 IU of vitamin D. Bone mineral density should be assessed every 2 years, and bisphosphonate therapy should be considered if the result is in the osteoporotic range. Patients with elevated lipid levels may be at risk for cardiovascular disease and can be considered for lipid-lowering therapy. Fat-soluble vitamin deficiencies should be treated with parenteral or water-soluble supplements. Liver transplant outcomes for patients with PBC are excellent, with a 1-year survival rate greater than 90% and a recurrence rate of approximately 20% at 5 years after liver transplantation. First-degree relatives of patients with PBC, especially women, should be screened by periodically checking ALP level.

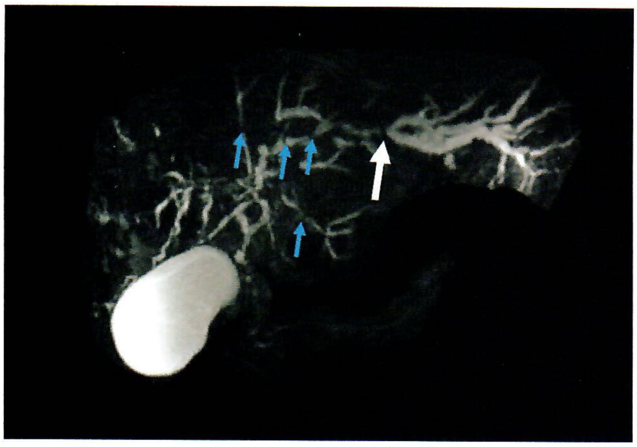

FIGURE 32. Magnetic resonance cholangiopancreatogram showing multifocal intrahepatic and extrahepatic bile duct stricturing (*blue arrows*) with a dominant left-lobe stricture (*white arrow*) and upstream bile duct dilation consistent with the diagnosis of primary sclerosing cholangitis.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is an autoimmune fibroinflammatory disease of the large bile ducts, but it can also affect the small bile ducts (small-duct PSC). It is more common in men than women, which is unique among the autoimmune liver diseases. PSC often presents without symptoms with a cholestatic pattern of liver enzyme abnormalities; pruritus may also be the presenting feature.

PSC can be diagnosed noninvasively through magnetic resonance cholangiopancreatography (MRCP) (**Figure 32**). Diagnosis does not usually require liver biopsy; small-duct PSC, which cannot be diagnosed by MRCP, is an exception. Endoscopic retrograde cholangiopancreatography (ERCP) should be considered in patients with jaundice, worsening pruritus, bacterial cholangitis, or a dominant stricture or bile duct mass on MRCP.

PSC is associated with inflammatory bowel disease (IBD) in about 85% of cases; up to 7.5% of patients with ulcerative colitis have PSC. All patients with PSC without known IBD should have a colonoscopy at the time of PSC diagnosis. Patients with concomitant IBD may have a unique PSC-IBD phenotype, characterized by rectal sparing, mild pancolitis, and backwash ileitis. This carries a higher risk for colon cancer, necessitating colonoscopy with surveillance biopsies every year from the time of diagnosis, as well as a higher risk for pouchitis after total colectomy.

Patients with PSC have a 15% lifetime risk for cholangiocarcinoma. Yearly MRCP and measurement of carbohydrate 19-9 are recommended for cholangiocarcinoma surveillance. The incidence of cholangiocarcinoma is highest in the first 2 years after PSC diagnosis. There is also an increased risk for gallbladder cancer in PSC; regular screening with ultrasonography should be considered. The management of gallbladder polyps is discussed in the Disorders of the Gallbladder and Bile Ducts chapter.

There is no effective medical therapy for PSC; it often requires liver transplantation and has the highest case-based mortality rate among the autoimmune liver diseases. In symptomatic patients, ERCP is used to dilate strictures and remove stones.

Median transplant-free survival for patients with PSC is 12 years. Transplantation should be considered for patients with decompensated cirrhosis, recurrent bacterial cholangitis, and hilar cholangiocarcinoma. Transplant outcomes for patients with PSC are excellent, with 1-year survival rates of at least 90% and recurrence rates of approximately 20% at 5 years after liver transplantation.

KEY POINTS

- For primary biliary cholangitis, ursodeoxycholic acid treatment results in histologic improvement, better survival rates, and diminished need for liver transplantation.
- Primary sclerosing cholangitis is associated with inflammatory bowel disease in about 85% of cases; these patients have an increased risk for colon cancer and require surveillance colonoscopy at diagnosis and every 1 to 2 years.
- Patients with PSC have a 15% lifetime risk for cholangiocarcinoma; annual MRCP and measurement of carbohydrate 19-9 are recommended for cholangiocarcinoma surveillance.

Classification of Liver Disease Severity

The Child-Turcotte-Pugh (CTP) score (**Table 36**) and MELD score (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/) are prognostic in patients with cirrhosis. The 1-year survival rates for CTP class A, B, and C cirrhosis are 100%, 80%, and 45%, respectively.

The MELD formula includes bilirubin level, INR, and creatinine level and is accurate in predicting 3-month mortality. Another version of the MELD score, the MELD-Na (www.mdcalc.com/meldna-meld-na-score-liver-cirrhosis), incorporates the sodium level. The MELD score was the basis for liver transplant allocation until 2016, when the allocation system was changed to include the MELD-Na score because it is a more predictive model of 3-month mortality.

The MELD score can estimate postoperative mortality in patients with cirrhosis (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis).

KEY POINT

- The Model for End-Stage Liver Disease-sodium formula accurately predicts 3-month mortality and is used for liver transplant allocation.

Complications of Advanced Liver Disease

Patients with chronic liver disease from any cause are at risk for cirrhosis. Compensated cirrhosis is uncomplicated and may be asymptomatic or associated with nonspecific symptoms. Patients with decompensated cirrhosis have complications such as ascites, hepatic encephalopathy, and variceal hemorrhage.

Portal Hypertension

Portal venous hypertension develops in the setting of advanced cirrhosis due to obstruction of blood flow caused by intrahepatic fibrosis, regenerating liver nodules, increased intrahepatic vascular resistance, and increased flow via the portal vein. Prehepatic causes, including portal vein thrombosis, and posthepatic causes, such as Budd-Chiari syndrome, can result in portal hypertension in the absence of cirrhosis. Complications of portal hypertension include gastroesophageal varices, ascites, and spontaneous bacterial peritonitis. The presence of these complications heralds a high rate of further complications and mortality and should prompt consideration of liver transplantation. See Vascular Diseases of the Liver for additional discussion of portal vein thrombosis and Budd-Chiari syndrome.

Esophageal Varices

Esophageal varices are enlarged vessels within the lumen of the lower esophagus that provide extrahepatic pathways of blood flow from the portal to the systemic circulation (**Figure 33**).

TABLE 36. Child-Turcotte-Pugh Score[a]

	1 Point	2 Points	3 Points
Encephalopathy	None	Grade I-II	Grade III-IV
Ascites	None	Mild/moderate	Severe
Bilirubin	<2 mg/dL (34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	>3 mg/dL (51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (28 g/L)
Prothrombin time above control/INR	<4 s/<1.7	4-6 s/1.7-2.3	>6 s/>2.3

[a] 5-6 points = Child-Turcotte-Pugh class A; 7-9 points = Child-Turcotte-Pugh class B; 10-15 points = Child-Turcotte-Pugh class C.

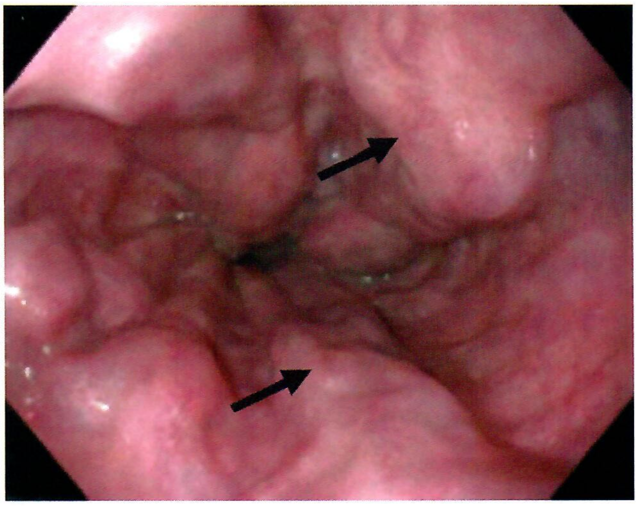

FIGURE 33. Endoscopic images of large esophageal varices with red wale marks characterized by erythematous raised areas (*arrows*). These varices are at risk for spontaneous hemorrhage and are an indication for prophylactic therapy.

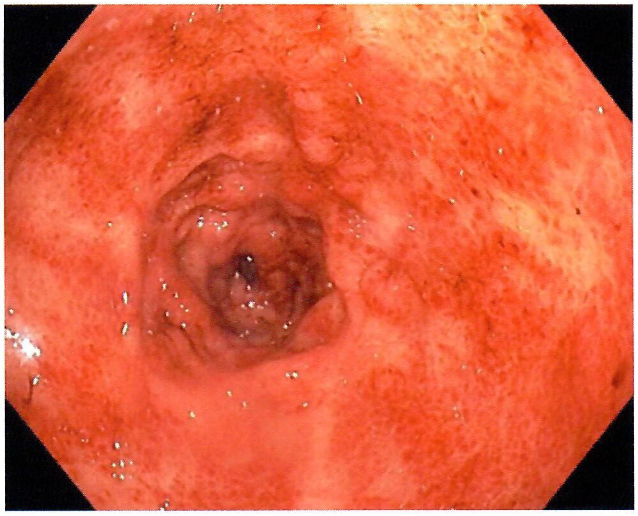

FIGURE 34. Endoscopic view of diffuse gastric antral vascular ectasias in the setting of portal hypertension.

If pressure in the lumen of a varix increases, esophageal varices enlarge and may spontaneously rupture, leading to bleeding, which may be massive. Treatment can reduce the risk for acute variceal hemorrhage and associated mortality. Upper endoscopy should be performed in all patients with cirrhosis to assess for varices. Management of varices in patients with cirrhosis depends on varix size and whether cirrhosis is compensated (**Table 37**).

See Gastrointestinal Bleeding for discussion of management and secondary prophylaxis of variceal hemorrhage.

Gastric Varices and Portal Hypertensive Gastropathy

Gastric varices are seen in up to 20% of patients with cirrhosis and are responsible for 10% to 30% of variceal hemorrhages. Varices that extend from the esophagus into the cardia of the stomach, along the lesser curvature of the stomach, are treated with band ligation, similar to esophageal varices. Varices of the gastric fundus or isolated varices in other parts of the stomach are generally not amenable to band ligation. Bleeding varices in these areas are treated with hemodynamic resuscitation, antibiotic therapy, and octreotide. A transjugular intrahepatic portosystemic shunt (TIPS) can be considered for bleeding from gastric varices. Balloon-occluded retrograde transvenous obliteration is another interventional radiologic procedure to eradicate gastric varices via the systemic circulation. Isolated gastric varices can occur with splenic vein thrombosis and are treated with splenectomy.

Portal hypertensive gastropathy is the presence of dilated mucosal gastric veins and venules and is a common endoscopic finding in patients with cirrhosis. It is rarely a cause of significant acute bleeding but may cause chronic blood loss. Treatment is centered on the underlying portal hypertension.

Gastric antral vascular ectasias consist of ectatic vessels that line the mucosa of the distal stomach. These can be present in patients without cirrhosis, but in the setting of portal hypertension, these mucosal lesions tend to be more diffuse (**Figure 34**) than the classic linear pattern ("watermelon stomach"). These are typically treated with endoscopic therapy, such as argon plasma coagulation. Portal decompressive interventions such as TIPS do not effectively treat gastric antral vascular ectasias.

Ascites

Ascites occurs in 50% of patients within 10 years of cirrhosis diagnosis and is the most common symptom of decompensated cirrhosis. Physical examination maneuvers can detect ascites, although they perform poorly compared with ultrasonography, which has high sensitivity for identifying ascites. When ascites is first detected, diagnostic paracentesis should

TABLE 37. Management of Screening-Detected Esophageal Varices in Patients With Compensated Cirrhosis

Findings	Management
No varices	Repeat upper endoscopy in 3 years (unless decompensation occurs)
Small varices (<5 mm)	Repeat upper endoscopy in 2 years (unless decompensation occurs)
Small varices with red wale marks (erythematous raised areas)	Initiate nonselective β-blocker therapy (propranolol, nadolol, or carvedilol)
Large varices (>5 mm)	Initiate nonselective β-blocker therapy or endoscopic variceal ligation
Varices in patients unable to tolerate β-blockers	Endoscopic variceal ligation

TABLE 38. Characteristics of Ascites

	SAAG	Ascitic Fluid Total Protein Level	Other Characteristics
Cirrhosis	High[a]	Low[b]	Clear, straw-colored
Heart failure	High[a]	High[c]	–
Chylous ascites	Low[d] or high[a]	High[c]	High triglycerides SAAG can be high if caused by portal hypertension SAAG is low if caused by lymphatic disruption
Tuberculosis	Low[d]	High[c]	Peritoneal biopsy may be required to confirm diagnosis of tuberculosis
Malignancy	Low[d]	High[c]	Positive cytology results
Nephrotic syndrome	Low[d]	Low[b]	Proteinuria and edema

SAAG = serum-ascites albumin gradient.

[a] ≥1.1 g/dL (11 g/L).

[b] <2.5 g/dL (25 g/L).

[c] ≥2.5 g/dL (25 g/L).

[d] <1.1 g/dL (11 g/L).

be performed. The serum–ascites albumin gradient is measured by subtracting the level of albumin in the ascitic fluid from the serum albumin measurement:

$$\text{serum–ascites albumin gradient} = \text{serum albumin} - \text{ascites albumin}$$

Total protein levels in ascitic fluid also help determine cause of the ascites. The characteristics of ascites are presented in **Table 38**.

In 85% of patients with ascites, the cause is cirrhosis. Management of ascites involves a sodium-restricted diet (<2 g/d). Diuretic therapy, typically with spironolactone and furosemide, is often required to assist natriuresis. Kidney function and electrolyte levels are checked 7 to 10 days after changes to diuretic regimens.

Paracenteses can be performed if ascites does not resolve with sodium restriction and diuretic therapy or if diuretic therapy is poorly tolerated. If more than 5 L of ascitic fluid is removed at one time, supplemental 25% albumin at a dose of 6 to 8 g/L of ascitic fluid removed should be administered to prevent circulatory dysfunction after paracentesis.

Patients with ascites should discontinue ACE inhibitors and NSAIDs. Intermittent paracentesis or TIPS can be considered in patients with refractory ascites and a low MELD score. Indwelling drains in ascites due to portal hypertension are not recommended because of high rates of complications, although they may be considered for end-of-life palliation.

Patients with ascites can develop pleural effusions (hepatic hydrothorax) because of permeability of the diaphragm and negative intrathoracic pressure. These effusions tend to be right-sided. Exclusion of other causes of pleural effusions is necessary. Management is similar to that for ascites, with dietary sodium restriction and diuretic therapy. Symptomatic hepatic hydrothorax may require thoracentesis or TIPS. Chemical pleurodesis is typically not beneficial. Indwelling chest tubes are not helpful and should be avoided because of the high risk for complications.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is an infection of portal hypertensive ascitic fluids. SBP can present with fever, abdominal pain, and/or kidney dysfunction; it should be considered in any patient with ascites whose clinical status declines. In patients with cirrhosis and ascites, long-term prophylactic antibiotic therapy, typically with a fluoroquinolone, is recommended to prevent SBP if the ascitic fluid protein level is less than 1.5 g/dL (15 g/L) and is associated with impaired renal function (serum creatinine ≥1.2 mg/dL [106.1 µmol/L], blood urea nitrogen ≥25 mg/dL [8.9 mmol/L], or serum sodium ≤130 mEq/L [130 mmol/L]) or liver failure (CTP score ≥9 and bilirubin level ≥3 mg/dL [51.3 µmol/L]).

SBP is diagnosed by an ascitic-fluid neutrophil count of 250/µL (0.25 × 10^9/L) or higher on diagnostic paracentesis. Bacterial culture of ascitic fluid, obtained after direct inoculation of fluid into culture bottles, should also be performed but is often negative. Prompt initiation of a third-generation cephalosporin is the initial treatment of SBP. Patients with kidney dysfunction or significant hepatic dysfunction (defined as serum bilirubin level >4 mg/dL [68 µmol/L]) should receive adjunctive albumin therapy (1.5 g/kg body weight on day 1 and 1 g/kg on day 3); such treatment has a survival benefit.

Follow-up paracentesis to demonstrate lessened inflammation can be performed if clinical improvement is not obvious. SBP commonly recurs, and indefinite secondary prophylactic therapy should be offered after SBP resolves, typically with once-daily fluoroquinolone therapy. Discontinuing nonselective β-blocker therapy, if present, should be considered because of the potential for increased mortality in patients with SBP. SBP has a high mortality rate, and patients who develop SBP should be considered for liver transplantation.

TABLE 39. Classification of Hepatic Encephalopathy

Severity of Encephalopathy	Description	Findings
Minimal	Detected only on neuropsychiatric testing	Few or absent clinical manifestations
Grade 1	Mild lack of awareness, sleep disturbances	Oriented to time and place, but with psychomotor slowing
Grade 2	Lethargic, disoriented, and with personality change	Disoriented to time, with asterixis
Grade 3	Somnolence, confusion, and significant disorientation	Disoriented to time, place, and situation, with asterixis
Grade 4	Coma	Lack of response even to painful stimuli

Adapted with permission from Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35. [PMID: 25042402] doi:10.1002/hep.27210. © 2014 by the American Association for the Study of Liver Diseases.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is brain dysfunction ranging from minimal abnormalities to frank coma. It results from insufficient hepatic function and portasystemic shunting of blood caused by portal hypertension. HE can develop spontaneously or be precipitated by other factors, such as infection, sedating medications, volume depletion, or gastrointestinal bleeding, and it heralds worsening liver function.

Detection of minimal HE manifestations requires neuropsychiatric testing, although overt changes of HE, ranging from personality changes to frank coma, are common in advanced cirrhosis (**Table 39**). Asterixis—a flapping hand tremor—is typically present in middle stages of hepatic encephalopathy. Asterixis is absent in subclinical hepatic encephalopathy and is lost as patients progress to later stages of hepatic encephalopathy, including coma.

Patients with severe hepatic encephalopathy should be monitored in an ICU. Diminishing consciousness should prompt consideration of intubation if airway-protective reflexes are lost.

Treatment of hepatic encephalopathy is multifaceted. Precipitating causes, such as infection or gastrointestinal bleeding, should be promptly treated, and sedating medications should be discontinued. Administration of the nonabsorbed disaccharide lactulose decreases absorption of nitrogenous substances and results in improvement in most patients. If response to lactulose therapy is suboptimal, rifaximin can be given to alter bacterial flora in the intestine. Although rifaximin is better tolerated than lactulose, it is often not first-line therapy because of its expense.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) occurs in the setting of portal hypertension and is due to reduced renal blood flow during simultaneous dilatation of the splanchnic vasculature. Most patients who develop HRS have cirrhosis, although alcoholic hepatitis and acute liver failure are also associated with HRS. Type 1 HRS is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) and/or 50% or greater from baseline within 48 hours, bland urinalysis, normal kidney ultrasonography findings, and exclusion of other causes of acute kidney injury (especially volume depletion). Patients have low fractional excretion of sodium and oliguria. Type 2 HRS is characterized by a gradual decline in kidney function associated with refractory ascites.

Declining renal function is one of the most important predictors of death in patients with cirrhosis. A rapid rise of serum creatinine should prompt evaluation for infections and causes of hypovolemia.

Management of HRS involves treatment of precipitating conditions, withdrawal of diuretics, and volume expansion with intravenous albumin. Vasoconstrictor treatment with midodrine and octreotide or norepinephrine to raise mean arterial pressure and improve renal perfusion may be useful. Treatment may also include intravenous albumin with either terlipressin (if available) or midodrine and octreotide to raise mean arterial pressure and improve kidney perfusion. Patients whose kidney function does not improve with therapy may require hemodialysis while they await liver transplantation.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is characterized by dilation of intrapulmonary vessels in patients with portal hypertension, resulting in right-to-left shunting of blood and hypoxemia. The dilated vessels reside in the inferior aspects of the lungs, and increased perfusion of these areas in the upright position results in orthodeoxia (worsening oxygen saturation while upright) and platypnea (worsening dyspnea when upright). The diagnosis should be suspected in patients with portal hypertension who have dyspnea and hypoxemia. Findings of intrapulmonary shunting upon agitated saline administration during echocardiography confirm the diagnosis. Macroaggregated albumin perfusion studies can also aid in diagnosis. HPS is initially treated with supplemental oxygen, but the only effective treatment is liver transplantation.

Portopulmonary Hypertension

Portopulmonary hypertension should be suspected in patients with cirrhosis and portal hypertension who present with dyspnea on exertion. Although less common than HPS, portopulmonary hypertension is a complication of advanced cirrhosis with a high mortality rate. Echocardiography demonstrates right ventricular systolic pressures greater than 50 mm Hg, which necessitates right-heart catheterization to confirm the diagnosis. Although portopulmonary hypertension was formerly a contraindication to liver transplantation, patients with preserved right ventricular function who attain a mean pulmonary artery pressure less than 35 mm Hg with vasodilator therapies can benefit from liver transplantation. Prostacyclin analogues, phosphodiesterase inhibitors, and endothelin receptor antagonists have been used to treat portopulmonary hypertension.

KEY POINTS

- Upper endoscopy should be performed in patients with cirrhosis to assess for esophageal varices; primary prophylaxis to prevent bleeding includes nonselective β-blocker therapy (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation.
- Precipitating causes of hepatic encephalopathy may include infection, sedating medications, volume depletion, or gastrointestinal bleeding; treatment involves addressing the precipitating cause and administering lactulose or rifaximin.
- HVC Ultrasonography is the most effective means of identifying ascites; the serum-ascites albumin gradient and total protein levels in ascitic fluid help determine the cause of ascites.
- Management of ascites involves a sodium-restricted diet and diuretic therapy.
- An ascitic-fluid neutrophil count of 250/µL (0.25×10^9/L) or greater confirms the diagnosis of spontaneous bacterial peritonitis; initial treatment is with a third-generation cephalosporin.
- Hepatopulmonary syndrome should be suspected in patients with portal hypertension who have dyspnea and hypoxemia; the diagnosis is confirmed by intrapulmonary shunting with agitated saline administration during echocardiography.

Health Care Maintenance in Patients With Chronic Liver Disease

Patients with chronic liver disease are at risk for severe complications if they develop acute hepatitis. They should be vaccinated against hepatitis A and B viruses if they are not immune. Nonresponse to vaccinations is more common in patients with cirrhosis, and postvaccination immunity should be assessed. Patients with chronic liver disease should receive annual influenza vaccination and pneumococcal vaccinations. Other vaccinations should be given based on current recommendations (see MKSAP 19 General Internal Medicine 2).

Patients with cirrhosis should be counseled to strictly avoid alcohol. Sedating medications, such as opiates and benzodiazepines, should be avoided to prevent hepatic encephalopathy. Patients should avoid consuming raw shellfish, which can transmit *Vibrio vulnificus*, an organism causing potentially fatal infection in patients with cirrhosis.

Metabolic bone disease is common in patients with cirrhosis, and patients should be screened for osteoporosis. The development of osteoporosis in patients with cirrhosis is multifactorial and is associated with jaundice (negatively affects osteoblast viability), hypogonadism, and decreased levels of insulin-like growth factor. Cholestasis also decreases absorption of vitamin D. Patients with osteoporosis are treated with calcium supplementation and antiresorptive agents. Patients with esophageal varices should receive intravenous rather than oral bisphosphonates. Patients with osteopenia should be treated with supplemental calcium plus vitamin D. Weight-bearing exercises are encouraged in patients with cirrhosis.

Protein-calorie malnutrition is common in patients with cirrhosis. Protein consumption is essential to prevent the catabolic effects of chronic liver disease. Patients with cirrhosis should consume 1.5 g of protein/d per kg of body weight.

Medications metabolized by the liver may require dosage adjustments depending on cirrhosis severity. Patients with advanced cirrhosis (CTP class B or C) often require dosage adjustments, whereas patients with well-compensated cirrhosis (CTP class A) may not.

Patients with advanced cirrhosis have complex analgesic prescribing needs. Narcotic analgesics can precipitate hepatic encephalopathy. NSAIDs can impair renal perfusion, worsen kidney function, and exacerbate fluid retention. Acetaminophen up to 2000 mg daily is generally safe in patients with cirrhosis. Alternative approaches to pain control, including nonpharmacologic options (e.g., physical therapy, behavioral therapy, and local injection therapies) as indicated, should be considered.

KEY POINTS

- Patients with chronic liver disease should be vaccinated against hepatitis A and B viruses and should receive pneumococcal vaccinations and annual influenza vaccination.
- Patients with cirrhosis should avoid alcohol, sedating drugs, opioids, and raw shellfish.
- Patients with cirrhosis should be screened for osteoporosis; confirmed osteoporosis should be treated with antiresorptive agents.

Solid and Cystic Liver Lesions

Benign liver lesions are typically discovered incidentally on abdominal imaging and are asymptomatic, with the exceptions of liver abscesses or some lesions greater than 5 cm. Most liver lesions are diagnosed noninvasively with CT or MRI. Percutaneous fine-needle aspiration of lesions is performed when imaging is nondiagnostic and when the information obtained from aspiration will prompt a change in management. Risks of liver biopsy, including bleeding, perforation, and death, are rare but must be considered.

Hepatic Cysts

Hepatic cysts are a common radiologic finding. Simple cysts are smooth with thin walls and anechoic features on ultrasonography. Patients with polycystic liver disease or autosomal dominant polycystic kidney disease can present with numerous liver cysts. Asymptomatic cysts are benign and require no follow-up. Large cysts rarely present with abdominal pain and can be treated with surgical defenestration or, if surgery is contraindicated, with cyst aspiration and sclerotherapy. Rarely, extensive polycystic liver disease may lead to portal hypertension due to vascular obstruction or malnutrition due to gastric compression. Management options include surgical debulking, but if this is not technically feasible, liver transplantation may be indicated. Cystadenomas are distinguished from simple cysts by the presence of thick, complex walls on ultrasonography; they require surgical resection because of risk for malignancy.

Hepatic Adenomas

Hepatic adenomas are rare liver neoplasms. They are associated with oral contraceptives and are eight times more common in women than men. Other risk factors include androgen treatment, type 1 and 3 glycogen storage disease, and obesity. Although benign, hepatic adenomas, especially larger ones, may rupture, with resultant hemorrhage, or undergo malignant transformation.

Hepatic adenomas can be incidentally found on ultrasonography, CT, or MRI. Hepatic adenomas can be differentiated from focal nodular hyperplasia with MRI with bile-excreted contrast material, such as gadobenate dimeglumine or gadoxetate disodium, because they typically do not have normal biliary excretion. Biopsy is indicated only when there is diagnostic uncertainty, but it may increase the risk for bleeding and should be performed only if the result will likely change management.

Treatment depends on use of oral contraceptives and adenoma size. All patients taking oral contraceptives should discontinue those drugs and undergo follow-up CT or MRI every 6 to 12 months to confirm stability or regression in lesion size. The duration of surveillance and treatment depends on subsequent imaging findings. In women not taking oral contraceptives, hepatic adenomas 5 cm or smaller can be managed with serial imaging every 6 months; however, with larger adenomas, the risk for hemorrhage or malignant transformation is elevated and surgical resection should be considered. Men with hepatic adenomas of any size are at increased risk for malignant transformation, and resection is recommended.

Pregnancy can result in adenoma growth, and resection or ablation of adenomas can be considered if pregnancy is contemplated.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is the most common benign liver tumor and a frequent incidental finding. It is caused by a congenital arterial anomaly leading to a focal area of regeneration that appears as a stellate scar on CT or MRI. CT or MRI with and without contrast can confirm the diagnosis. FNH does not have malignant potential or risk for bleeding and does not require follow-up. In women with FNH who continue to use oral contraceptives, there is limited evidence to recommend liver ultrasonography every 2 to 3 years to assess for growth.

Hepatic Hemangiomas

Hepatic hemangiomas are benign, common, and more frequent in women. Up to 20% of affected patients have multiple hemangiomas. Hepatic hemangiomas are rarely symptomatic, and, in most cases, symptoms that might be ascribed to a hemangioma are due to other causes. Hemangiomas do not have potential for malignancy, and spontaneous bleeding is rare. The diagnosis should be confirmed with MRI or CT with contrast, which typically shows peripheral nodular enhancement and progressive centripetal contrast enhancement. Biopsies should be avoided because of bleeding risk. Hepatic hemangiomas do not require intervention or follow-up except in the rare instance when they cause symptoms.

Hepatic Abscesses

Pyogenic Liver Abscesses

Pyogenic liver abscesses are complications of biliary tract infections or portal venous spread of intra-abdominal infections, such as diverticulitis. Patients with pyogenic liver abscesses present with fever, right-upper-quadrant pain, and malaise. Liver abscesses are typically polymicrobial, and the diagnosis is confirmed by radiologically guided aspiration. Small abscesses (<3 cm) can be successfully treated by administration of broad-spectrum antibiotics. Larger abscesses are treated by aspiration or longer-term percutaneous catheter drainage in addition to broad-spectrum antibiotics. Radiologically guided aspiration with catheter drainage is usually successful; surgical excision of pyogenic hepatic abscesses is rarely needed.

Amebic Liver Abscesses

Amebic abscesses of the liver are found in developing areas of the world or in persons who have emigrated from countries where amebiasis is endemic. Intestinal infection with amoebae can result in invasion of the portal vein and migration to the liver. Symptoms of amebic liver abscesses include right-upper-quadrant abdominal pain and fever. Amebic liver abscess is diagnosed by hepatic imaging and serologic testing; aspiration is usually not required. Treatment of the hepatic infection with metronidazole or tinidazole should be accompanied by eradication of the always-coexistent intestinal infection with paromomycin.

Hepatic Granulomas

Granulomas are focal inflammatory lesions that consist of mononuclear cells, lymphocytes, and fibroblasts. Hepatic granulomatous disease can be seen with infections, such as tuberculosis, fungal infection (e.g., coccidioidomycosis, histoplasmosis), Q fever, cytomegalovirus infection, Epstein-Barr virus infection, and viral hepatitis. Granulomas also occur with inflammatory disorders (e.g., sarcoidosis), medications (e.g., allopurinol), and malignancies (e.g., lymphoma).

Symptoms of hepatic granulomas are nonspecific and include fever, malaise, and night sweats in addition to symptoms seen with the underlying disorder. Hepatic sarcoidosis may occur in patients with other systemic manifestations of sarcoidosis but can be the only manifestation of sarcoidosis (for further discussion of sarcoidosis, see MKSAP 19 Rheumatology). Portal hypertension can result from obliteration of small portal veins. In patients with hepatic sarcoidosis, 6% to 8% progress to cirrhosis, although liver failure and the need for liver transplantation are rare.

Alkaline phosphatase and aminotransferase levels can be elevated regardless of cause. No single test can diagnose hepatic sarcoidosis. Biopsy may be necessary in specific instances.

Treatment of hepatic granulomas depends on the cause. Infectious causes should be treated if identified. Potential offending medications should be discontinued.

Treatment of hepatic sarcoidosis is not necessary if there are no symptoms and liver chemistries are only mildly elevated. Ursodeoxycholic acid or glucocorticoids may be considered if symptoms exist or liver chemistries are substantially elevated.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common liver tumor in patients with cirrhosis, the fifth most common cause of cancer worldwide, and the second most common cause of cancer-related death worldwide. More than 80% of patients with HCC have cirrhosis.

Patients with cirrhosis, regardless of cause, require surveillance liver ultrasonography with or without α-fetoprotein measurement every 6 months. This approach leads to early diagnosis, increased rate of curative treatment, and improved 3-year survival rates. Patients with HBV infection can develop HCC even without cirrhosis. Surveillance for HCC is recommended even in the absence of cirrhosis in individuals with HBV who are at high risk (patients with a family history of HCC, patients from sub-Saharan Africa and age >20 years, Asian men >40 years, and Asian women >50 years) (**Table 40**).

HCC is typically diagnosed without biopsy with the use of multiphase contrast-enhanced CT or MRI in patients with cirrhosis and a lesion measuring at least 1 cm. Biopsy may be needed for lesions that are indeterminant on imaging.

Many societies have issued guidelines for managing HCC. Patients with CTP class A cirrhosis, without significant portal hypertension or jaundice, and with a singular lesion 5 cm or smaller should be considered for curative resection. Liver transplantation should be considered in patients with HCC meeting the Milan criteria and with portal hypertension or jaundice. The Milan criteria are as follows: up to three liver lesions 3 cm or smaller or one lesion 5 cm or smaller, without apparent vascular invasion and without extrahepatic spread. Patients with a tumor burden that exceeds the Milan criteria can potentially undergo locoregional therapy to "downsize" tumor burden to within Milan criteria, permitting consideration of liver transplantation. Locoregional therapies include radiofrequency or microwave ablation, transarterial chemoembolization, and transarterial radioembolization. Patients who are not surgical or liver transplant candidates should be considered for locoregional therapy if they lack macrovascular invasion (tumor thrombus) or extrahepatic spread. Decisions about locoregional therapy are increasingly made through multidisciplinary tumor boards.

Systemic therapy options for patients with macrovascular invasion or evidence of extrahepatic disease have been developed. Sorafenib, an oral multikinase inhibitor, provides a modest survival benefit in patients who have HCC with macrovascular invasion or metastatic disease. Other FDA-approved drugs for advanced HCC include lenvatinib, regorafenib, and nivolumab; the latter is an intravenous humanized monoclonal antibody against the programmed cell death receptor. The FDA has approved the combination of atezolizumab and bevacizumab as therapy for hepatocellular carcinoma.

TABLE 40. Populations Recommended for Hepatocellular Carcinoma Screening and Surveillance[a]

Cirrhosis
Asian descent + male sex + age >40 years in HBV-infected patients
Asian descent + female sex + age >50 years in HBV-infected patients
Sub-Saharan African descent + age >20 years in HBV-infected patients
Persistent inflammatory activity (defined as elevated ALT level and HBV DNA level >10,000 IU/mL for at least a few years) in HBV-infected patients
Family history of hepatocellular carcinoma in HBV-infected patients
Males with primary biliary cholangitis

ALT = alanine aminotransferase; HBV = hepatitis B virus.

[a] Hepatocellular carcinoma screening should be performed with ultrasonography with or without α-fetoprotein every 6 months. Cross-sectional imaging can be used in cases in which ultrasonography is unreliable or is expected to be unreliable.

KEY POINTS

- Asymptomatic hepatic cysts are benign and require no follow-up. **HVC**
- Patients with hepatic adenomas taking oral contraceptives should discontinue those drugs and undergo follow-up imaging to confirm stability or regression in lesion size.

(Continued)

KEY POINTS ***(continued)***

HVC
- Focal nodular hyperplasia does not have malignant potential or a risk for bleeding and does not require follow-up.
- Patients with cirrhosis and high-risk patients with hepatitis B virus infection require hepatocellular carcinoma surveillance using liver ultrasonography with or without α-fetoprotein measurement every 6 months.

Liver Transplantation

Referral for liver transplantation is indicated in patients whose MELD score is 15 or greater because transplantation provides a survival advantage in these patients. Patients with decompensated cirrhosis, including ascites, spontaneous bacterial peritonitis, esophageal variceal bleeding, hepatic encephalopathy, jaundice, or hepatocellular carcinoma, should also be considered for referral. Patients should generally be abstinent from alcohol, although transplant centers may differ in their requirements for sobriety duration and chemical-dependency treatment. Other factors important in candidate selection include adequate social support, ability to adhere to medical treatment, and absence of significant cardiopulmonary and psychiatric comorbidities and active infectious diseases.

Appropriate candidates are placed on the national waiting list, with the highest priority given to patients with acute liver failure and high MELD-Na scores. MELD exception points may also be added in the presence of specific disorders, including hepatocellular carcinoma, portopulmonary hypertension, hepatopulmonary syndrome, familial amyloidotic polyneuropathy, primary hyperoxaluria, cystic fibrosis, and cholangiocarcinoma.

The average 1- and 5-year survival rates after liver transplantation are 92% and 75% to 85%, respectively. Recipients require lifelong immunosuppression, most commonly with tacrolimus or cyclosporine. Recipients have increased risk for diabetes, hypertension, hyperlipidemia, chronic kidney disease, and malignancy secondary to immunosuppressive medications.

KEY POINT

- Referral to a transplant center is indicated for patients with acute liver failure or patients with cirrhosis with a Model for End-Stage Liver Disease score of 15 or greater or evidence of decompensated cirrhosis.

Pregnancy-Related Liver Diseases

Pregnancy results in physiologic changes that mimic chronic liver disease. Altered hormonal states and increasing circulatory volume can lead to lower-extremity edema, palmar erythema, and spider angiomata.

Pregnant women with preexisting HCV and HBV infection can transmit the virus to the newborn. Vertical transmission of HCV, however, is relatively rare; less than 5% of women with HCV viremia transmit HCV to their children. No specific steps can be taken to eliminate the risk for vertical transmission of HCV. Antiviral therapy for HCV should not be undertaken during pregnancy.

HBV carries a higher risk for vertical transmission, which can be as high as 90% among women with HBe antigen-positive infection; high HBV DNA levels also increase the risk for transmission. Pregnant women with an HBV DNA level exceeding 200,000 IU/mL between gestational weeks 24 and 28 should start oral antiviral treatment to prevent vertical transmission. Oral antiviral agents approved in pregnancy include lamivudine, telbivudine, and tenofovir. Breastfeeding is not contraindicated during antiviral treatment. Passive immunization with HBV immune globulin and active HBV vaccination should be administered to newborns within 12 hours of delivery. These measures reduce vertical transmission rates by 95%.

Women with autoimmune hepatitis who become pregnant typically continue using prednisone and/or azathioprine, which are considered safe during pregnancy. The risk for a flare of autoimmune hepatitis due to stopping these medications is considered a greater risk.

Several liver diseases are unique to pregnancy and can affect the health of mother and fetus. During the first trimester, hyperemesis gravidarum occurs when prolonged, intractable vomiting results in fluid and electrolyte abnormalities. Hepatic aminotransferase levels are elevated in up to 50% of cases of hyperemesis gravidarum, but jaundice is rare. Laboratory abnormalities typically resolve when vomiting abates. Pyridoxine and antiemetic medications can alleviate symptoms of hyperemesis gravidarum.

Intrahepatic cholestasis of pregnancy is presumed to result from cholestatic effects of increased levels of pregnancy-related hormones. Risk for this condition can be elevated in women of South American descent, women pregnant with twins, and women with a history of liver disease. Intrahepatic cholestasis of pregnancy typically presents in the second to third trimesters. Symptoms include pruritus in most patients and jaundice in 10% to 25%. Serum bile acid levels are elevated and help establish the diagnosis. Fetal complications, including placental insufficiency, premature labor, and sudden fetal death, are more common in intrahepatic cholestasis of pregnancy. Ursodeoxycholic acid relieves pruritus and improves fetal outcomes. Fetal mortality is increased late in gestation. Delivery is typically induced at 36 to 38 weeks' gestation in women with proven disease.

The most serious pregnancy-related liver diseases are HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome and acute fatty liver of pregnancy. They occur in the third trimester of pregnancy and are associated with high rates of maternal and fetal mortality. Definitive therapy for these conditions is delivery of the fetus.

HELLP syndrome is a severe complication of preeclampsia. It typically presents with abdominal pain, nausea with vomiting, pruritus, and jaundice. Blood pressure, fluids and electrolytes, kidney function, and coagulopathy may require careful management in the perinatal state; patients should be managed in high-risk obstetric units. Although delivery is the definitive therapy, the maternal condition may continue to worsen in the immediate postpartum period. Resolution typically occurs within days after delivery. Rarely, liver transplantation may be required if liver recovery is not seen. HELLP can recur in up to 25% of subsequent pregnancies.

Acute fatty liver of pregnancy presents with symptoms similar to those of HELLP syndrome. Indicators of liver failure, including hypoglycemia and coagulopathy, can be seen. Affected patients may require transfer to a liver transplant center. Prompt delivery of the fetus once the diagnosis is recognized typically results in improvement of the mother's medical condition in 48 to 72 hours. Acute fatty liver of pregnancy can recur in subsequent pregnancies. It is associated with long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency, and affected women and their offspring should be screened for this deficiency.

KEY POINTS

- Measures to reduce vertical transmission of hepatitis B virus include administering hepatitis B virus immune globulin and immediate vaccination of newborns.
- The most serious liver complications of pregnancy occur in the third trimester and include HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome and acute fatty liver of pregnancy; both are managed in high-risk obstetric units and with early delivery.

Vascular Diseases of the Liver

Portal Vein Thrombosis

Portal vein thrombosis is common in patients with decompensated cirrhosis and is due to slow flow through the portal veins rather than hypercoagulability; it may occasionally occur in patients without cirrhosis. It is typically diagnosed by abdominal Doppler ultrasonography; contrast-enhanced CT or MRI should be completed to delineate extent of thrombosis and to assess for tumor thrombosis. Chronic portal vein thrombosis is typically asymptomatic and does not usually require anticoagulant therapy unless thrombophilia, bowel ischemia, or progression of thrombus is present. Patients with acute portal vein thrombosis should receive anticoagulation unless risk of bleeding is very prohibitive. Direct oral anticoagulants or low-molecular-weight heparin are the anticoagulants of choice. Systemic thrombolytic therapy and catheter-directed thrombolysis are rarely indicated.

Budd-Chiari Syndrome

Budd-Chiari syndrome describes any disease process that obstructs the normal outflow of blood from the liver, usually as thrombosis of the hepatic veins. The syndrome may be associated with myeloproliferative neoplasms, pregnancy, oral contraceptive use, inflammatory bowel disease, or inherited thrombophilias. Underlying malignancy, especially hepatocellular carcinoma, may also be causative. Characteristic symptoms include hepatomegaly, ascites, and right-upper-quadrant abdominal pain. Budd-Chiari syndrome is typically diagnosed by Doppler ultrasonography in the appropriate clinical setting. The caudate lobe of the liver is hypertrophied because caudate venous outflow is directly into the inferior vena cava rather than through the hepatic veins. Long-term anticoagulation is required in patients with Budd-Chiari syndrome, although bleeding risks are significant in patients with acute or chronic liver disease, portal hypertension, and esophageal varices. Angioplasty of the hepatic veins and/or TIPS placement can be used to reestablish adequate hepatic venous drainage. If liver failure develops, liver transplantation may be considered.

KEY POINTS

- Portal vein thrombosis is common in patients with decompensated cirrhosis and is a consequence of poor flow through the portal veins.
- Characteristic symptoms of Budd-Chiari syndrome include hepatomegaly, ascites, and right-upper-quadrant abdominal pain.

Disorders of the Gallbladder and Bile Ducts

Asymptomatic Gallstones

Gallstones can be characterized as cholesterol stones or pigment stones. Cholesterol stones result from supersaturation of bile with cholesterol; they account for approximately 75% of gallstones in the United States. Risk factors for cholesterol stones include older age, female sex (twice as likely in women as in men), American Indian ethnicity, Western diet, pregnancy, rapid weight loss, obesity, total parenteral nutrition, and estrogen supplementation. Predisposing factors for pigment stones include chronic hemolysis, ineffective erythropoiesis, Crohn disease, cirrhosis, biliary stasis, and bacterial biliary infections.

Gallstones are commonly discovered at abdominal ultrasonography (**Figure 35**) and CT performed for unrelated reasons.

Incidental gallstones are typically asymptomatic, and prophylactic cholecystectomy is generally not recommended. Cholecystectomy is indicated in asymptomatic patients with characteristics posing a high risk for gallbladder cancer: gallstones larger than 3 cm, porcelain gallbladder (intramural calcification of gallbladder wall), or gallbladder polyps larger than 1 cm.

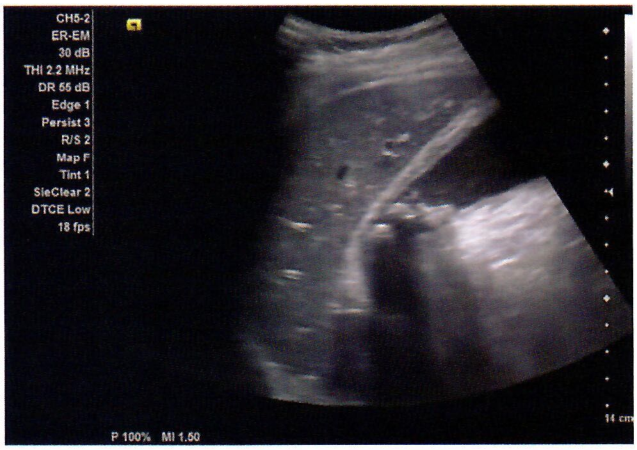

FIGURE 35. Ultrasound shows the liver (*left*) and the gallbladder in long axis with multiple stones present. The stones appear hyperechoic (*white*) with shadowing artifact posteriorly, consistent with cholelithiasis. The lumen of a normal gallbladder should appear anechoic (*black*). It is important to scan through the gallbladder to ensure that the entire lumen is visualized before determining whether stones are absent. An indeterminate study would occur if the gallbladder cannot be completely visualized, usually because of underdistention secondary to lack of fasting.

KEY POINT

HVC
- Asymptomatic gallstones discovered incidentally do not require cholecystectomy except in the setting of a high risk for gallbladder cancer (gallstones >3 cm, porcelain gallbladder, or gallbladder polyps >1 cm).

Biliary Colic

Biliary colic results from contraction of the gallbladder in the presence of an obstructed cystic duct, usually by a gallstone. Pain is typically of acute onset, lasts 30 minutes to 6 hours, is severe and steady, and is located in the right upper quadrant or epigastrium. Pain may radiate to the right shoulder and is associated with nausea, vomiting, and diaphoresis. Symptoms may be precipitated by meals, which cause gallbladder contraction. Constant, unremitting abdominal pain is not usually associated with biliary colic.

Patients with typical biliary colic symptoms and gallstones on imaging should undergo cholecystectomy because of an increased risk for future complications, including choledocholithiasis, cholangitis, and pancreatitis.

KEY POINT

- Patients with typical biliary colic symptoms and gallstones on imaging should undergo cholecystectomy.

Acute Cholecystitis

Acute cholecystitis is due to cystic duct obstruction and gallbladder inflammation, often accompanied by gallbladder infection. Patients present with severe right-upper-quadrant or epigastric pain lasting longer than 6 hours, with fever and tenderness in the right upper quadrant. A positive Murphy sign may be present. Laboratory studies may show leukocytosis; liver chemistries are often normal or minimally elevated unless complications such as common bile duct obstruction or cholangitis are present. Acute cholecystitis is suggested by ultrasound showing gallbladder wall thickening and/or edema and a sonographic Murphy sign (arrest of respiration with compression by the ultrasound probe). Lack of gallbladder filling on hepatobiliary iminodiacetic acid scanning supports this diagnosis. This test is appropriate in the setting of a high clinical likelihood of acute cholecystitis but a negative or indeterminate ultrasound finding.

Treatment includes analgesia, intravenous antibiotics with gram-negative and anaerobic coverage, and cholecystectomy. Emergency surgery is necessary for suspected gallbladder perforation or emphysematous cholecystitis (infection of the gallbladder wall with gas-forming organisms, such as *Clostridium perfringens*). Most patients should undergo cholecystectomy during initial hospitalization. Patients with high surgical risk who respond to antibiotics can be reassessed later to determine whether their surgical risk has decreased. In patients who are not good surgical candidates and do not respond to antibiotics, percutaneous cholecystostomy tube or endoscopic drainage can be pursued.

KEY POINTS

HVC
- Cholecystitis can be diagnosed by suggestive clinical findings and ultrasound showing gallbladder-wall thickening or edema and sonographic Murphy sign.
- Treatment of acute cholecystitis includes analgesia, intravenous antibiotics with gram-negative and anaerobic coverage, and cholecystectomy during initial hospitalization; percutaneous cholecystostomy tube or endoscopic drainage can be pursued in patients with high surgical risk.

Acalculous Cholecystitis

Acalculous cholecystitis typically occurs in critically ill patients and results from gallbladder ischemia, which can be complicated by enteric bacterial infection. Risk factors include cardiac surgery, sepsis, burns, and vasculitis. In alert patients, the presentation is pain, similar to that seen in cholecystitis related to gallstones. In sedated or mechanically ventilated patients, it may present with leukocytosis, jaundice, and sepsis. Diagnosis is made with ultrasound showing gallbladder-wall thickening, pericholecystic fluid, gallbladder distention, or gallbladder-wall pneumatosis without stones (**Figure 36**).

Treatment entails intravenous antibiotics to cover enteric bacteria and cholecystectomy. A percutaneous cholecystostomy tube may be needed for unstable patients or poor surgical candidates. Endoscopic gallbladder drainage can be considered. The mortality rate for untreated acalculous cholecystitis is as high as 75%.

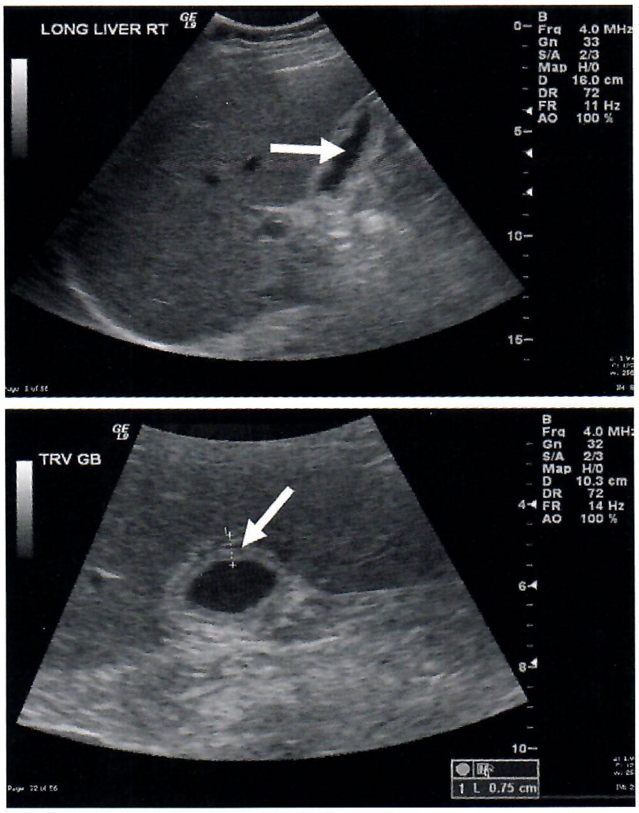

FIGURE 36. Gallbladder ultrasound consistent with acalculous cholecystitis showing a thickened gallbladder wall (*bottom*), pericholecystic fluid (*top*), and an absence of gallstones or sludge.

KEY POINTS

- Acalculous cholecystitis typically occurs in critically ill patients and results from gallbladder ischemia, which can be complicated by enteric bacterial infection.
- In alert patients, the presentation is pain, similar to that seen in cholecystitis; in sedated or mechanically ventilated patients, it may present with leukocytosis, jaundice, and sepsis.

Functional Gallbladder Disorder

Functional gallbladder disorder should be considered in patients with biliary pain without gallstones or structural pathology. Other causes of upper abdominal discomfort, including peptic ulcer disease and angina, should be considered. A gallbladder ejection fraction less than 40% as measured by cholecystokinin-stimulated cholescintigraphy supports the diagnosis but may not predict response to cholecystectomy. Reassurance and antispasmodic agents may be of benefit. If no other cause of pain is found, pain recurs, and the gallbladder ejection fraction is less than 40%, then cholecystectomy can be considered. In clinical practice, patients who meet these criteria and undergo cholecystectomy may continue to have similar upper abdominal symptoms postoperatively.

Common Bile Duct Stones and Cholangitis

Common bile duct stones are a leading cause of obstructive jaundice and pancreatitis. Although 20% of common duct stones pass spontaneously and less than 50% of patients develop symptoms, stone extraction should be offered to most patients. Symptoms of common bile duct stones include jaundice and abdominal pain due to obstruction of bile flow. Common duct stones may be visualized by transabdominal ultrasonography. In the absence of visualization, an elevated serum bilirubin level and dilated common duct on ultrasonography suggest the diagnosis. Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred method for stone extraction and should be performed in patients with a high likelihood of choledocholithiasis (**Figure 37**). In patients who are suspected of having common duct stones but have indeterminate findings on ultrasonography, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography should be performed to avoid ERCP risks. Cholecystectomy should be performed within 2 weeks of stone extraction.

Cholangitis is infection of the biliary tree, usually in the setting of biliary stasis or obstruction. Symptoms include fever, jaundice, and right-upper-quadrant pain (Charcot triad). Cholangitis is potentially life-threatening; antibiotics targeting gram-negative Enterobacteriaceae should be administered immediately. Common bile duct stones should be removed urgently with ERCP in patients with cholangitis, after which elective cholecystectomy should be performed during initial hospitalization to reduce the risk for complications. In patients who are not surgical candidates, endoscopic sphincterotomy can facilitate passage of additional common bile duct stones.

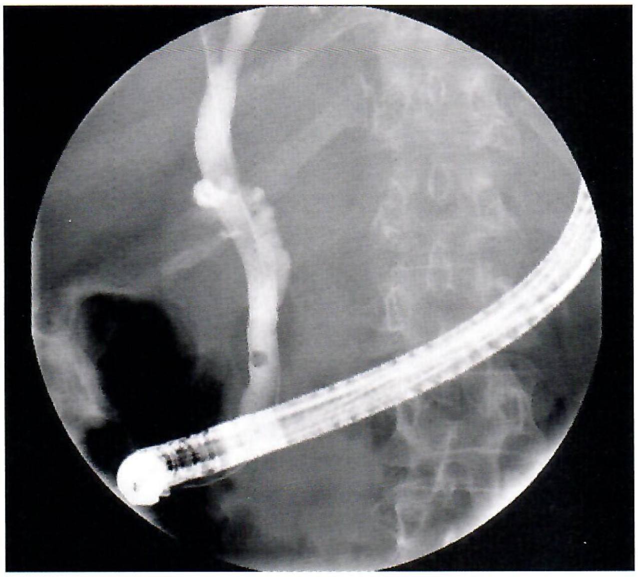

FIGURE 37. Choledocholithiasis is seen on endoscopic retrograde cholangiopancreatography, which shows an approximately 5 mm, round opacity in the distal common bile duct consistent with a stone.

KEY POINTS

- Symptoms of cholangitis include fever, jaundice, and right-upper-quadrant pain
- Endoscopic retrograde cholangiopancreatography is the preferred method for relieving obstruction due to a common bile duct stone.
- Cholangitis is potentially life-threatening; antibiotics targeting gram-negative Enterobacteriaceae should be administered immediately, and identified common bile duct stones should be removed urgently.

Gallbladder Polyps

Gallbladder polyps are usually found incidentally and can be seen on 1% to 5% of gallbladder ultrasounds. Neoplastic adenomas represent less than 0.5% of polyps. The best predictor of a malignant lesion is size, with polyps 1 cm or greater more likely to be neoplastic. Gallbladder polyps associated with gallbladder stones or primary sclerosing cholangitis are also more likely to be neoplastic. Management of gallbladder polyps is outlined in **Figure 38**.

KEY POINT

- Gallbladder polyps 1 cm or greater and those associated with gallbladder stones or primary sclerosing cholangitis are more likely to be neoplastic and should prompt consideration of cholecystectomy.

Gallbladder Cancer

Gallbladder cancer is the most common biliary cancer in the United States, but it is rare, with an incidence of 1 to 2 cases per 100,000. The gallbladder is a reservoir for *Salmonella typhi* in chronically infected patients, and these patients are at higher risk for gallbladder cancer.

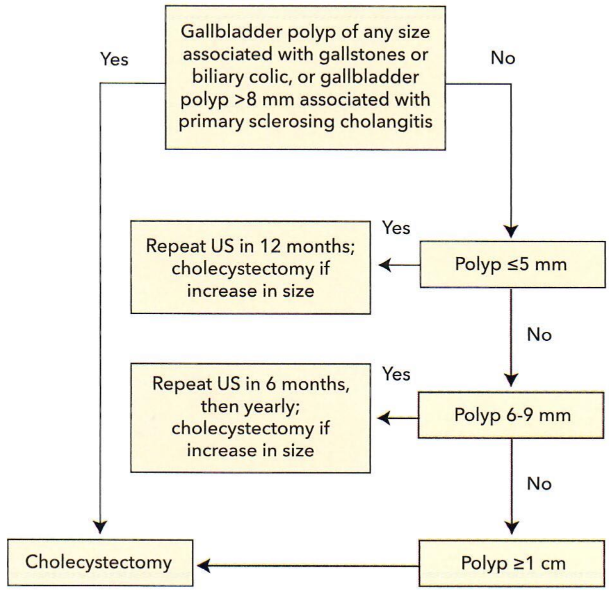
Gallbladder polyp of any size associated with gallstones or biliary colic, or gallbladder polyp >8 mm associated with primary sclerosing cholangitis
Yes
No
Polyp ≤5 mm
Yes
Repeat US in 12 months; cholecystectomy if increase in size
No
Polyp 6-9 mm
Yes
Repeat US in 6 months, then yearly; cholecystectomy if increase in size
No
Polyp ≥1 cm
Cholecystectomy

FIGURE 38. Management of gallbladder polyps.

Symptoms include biliary colic in early cancer and right-upper-quadrant pain, nausea, vomiting, weight loss, or jaundice in advanced cancer. Gallbladder cancer should be suspected if a mass is seen on CT or MRI.

Early gallbladder cancer is most commonly diagnosed incidentally when cholecystectomy is performed for biliary colic. Incidental tumors invading the lamina propria (stage T1a) do not require further treatment; more advanced lesions require more extensive surgery.

Treatment of choice for gallbladder cancer is surgery. Unresectable disease is treated with chemotherapy with or without radiation or with palliative care.

Cholangiocarcinoma

Cholangiocarcinoma is rare but has become an increasingly recognized malignancy over the last four decades. The three types are intrahepatic, perihilar, and distal: The intrahepatic type is seen in bile ducts within the liver parenchyma; the perihilar type, at the confluence of right and left hepatic ducts; and the distal type, in the extrahepatic bile duct distal to the cystic duct. Risk factors for cholangiocarcinoma include primary sclerosing cholangitis, choledochal cysts, liver flukes, thorium dioxide exposure, metabolic syndrome, and hepatolithiasis. Symptoms, including jaundice, right-upper-quadrant pain, and constitutional symptoms, typically develop only with advanced-stage disease.

Diagnosis of intrahepatic cholangiocarcinoma requires CT or MRI and, typically, biopsy confirmation. An elevated CA 19-9 level is supportive but insufficient for diagnosis. First-line therapy for intrahepatic cholangiocarcinoma is resection. Locoregional therapies, including transarterial chemoembolization, radioembolization, or external-beam radiation, may be options if patients are not candidates for resection. Chemotherapy may be offered to patients who are not candidates for surgical or locoregional therapies.

Perihilar cholangiocarcinoma can be difficult to diagnose and may require both MRCP and ERCP. During ERCP, bile-duct brushings are obtained for cytologic examination. Fluorescence in situ hybridization may help diagnostically. Serial ERCP may be required every 2 to 3 months for diagnosis. First-line therapy is resection. Patients with unresectable perihilar cholangiocarcinoma smaller than 3 cm and without extrahepatic spread can be evaluated for liver transplantation at centers with neoadjuvant chemoradiation protocols. In patients with perihilar cholangiocarcinoma, percutaneous or transluminal biopsy excludes liver transplantation because of the risk for tumor seeding.

Distal cholangiocarcinoma is diagnosed by the same modalities as for perihilar cholangiocarcinoma. Preferred treatment is pancreaticoduodenectomy.

Because of late symptom development, 5-year survival for patients with cholangiocarcinoma (except liver transplant recipients), including those who undergo resection, is low (20% to 30%).

KEY POINTS

- Resection is first-line treatment for cholangiocarcinoma.
- Selected patients with unresectable perihilar cholangiocarcinoma smaller than 3 cm and without extrahepatic spread may be candidates for liver transplantation.

Gastrointestinal Bleeding

Overview

In the United States, gastrointestinal bleeding is a common gastrointestinal cause of hospitalization. Upper gastrointestinal bleeding (UGIB) is defined as bleeding from the esophagus, stomach, or duodenum. The mortality rate for patients with UGIB varies from 2% to 10%, with much of the mortality occurring in patients with significant comorbid medical conditions. Lower gastrointestinal bleeding (LGIB) occurs in the colon or anorectum. It is less common, is typically less severe, and has a lower mortality rate than UGIB. Suspected small-bowel bleeding, in which bleeding does not appear to originate from the upper or lower gastrointestinal tract following upper and lower endoscopy, accounts for less than 10% of gastrointestinal bleeding. In 25% of these patients, however, the upper or lower gastrointestinal source of bleeding was missed on initial endoscopy.

KEY POINT

- Upper gastrointestinal bleeding is more common, is more severe, and has a higher mortality rate than lower gastrointestinal bleeding.

Upper Gastrointestinal Bleeding

UGIB can present in various ways: hematemesis (vomiting of bright red blood or clots), coffee-ground emesis (vomiting of dark granular material resulting from the action of gastric acid on blood), melena (black, tarry stool with a distinctive odor), and hematochezia (passage of red blood or clots from the rectum).

Causes

Common causes of UGIB include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear. Peptic ulcer disease is the most common cause (50%), with most gastroduodenal ulcers caused by *Helicobacter pylori* or NSAID use. Erosive esophagitis is a common endoscopic finding but infrequently causes clinically important UGIB. Therefore, in a patient with significant UGIB and erosive esophagitis, alternative causes for the bleeding should be sought.

Bleeding gastroesophageal varices typically occur in the distal esophagus or proximal stomach in individuals with advanced liver disease. Bleeding risk of varices is proportional to varix size.

A Mallory-Weiss tear is a mucosal disruption at the gastroesophageal junction and typically forms after repeated episodes of severe vomiting or retching.

Less common causes of UGIB are listed in **Table 41**.

TABLE 41. Less Common Causes of Upper Gastrointestinal Bleeding

Lesion	Pathogenesis	Presentation	Treatment
Cameron erosion	Mechanical trauma to mucosal folds of hiatal hernia	Typically chronic GI bleeding presenting as iron deficiency anemia	Includes medical therapy with PPI and iron; surgical repair of hiatal hernia
Dieulafoy lesion	Dilated, aberrant submucosal vessel	Included in differential diagnosis of recurrent, often massive bleeding without clear source	Endoscopic
Gastric antral vascular ectasia	Most idiopathic; some associated with cirrhosis and systemic sclerosis	Acute bleeding or iron deficiency anemia	Endoscopic
Aortoenteric fistula	Direct communication between aorta and GI tract	"Herald" bleeding followed by massive exsanguination	Surgical
Hemosuccus pancreaticus	Erosion of pancreatic pseudocyst or tumor into a vessel with bleeding into pancreatic duct	Upper GI bleeding in setting of pancreatic disease	Mesenteric angiography with coil embolization
Hemobilia	Bleeding from the hepatobiliary tract often caused by arteriobiliary fistula from trauma or liver biopsy	Triad of jaundice, biliary colic, and GI bleeding	Angiography or surgical
Upper GI tumors	Benign or malignant neoplasms	Slow or massive hemorrhage	Palliative radiographic, endoscopic techniques, surgery
Portal hypertensive gastropathy	Portal hypertension	Usually slow/chronic blood loss; occasionally significant hemorrhage	Medical therapy (β-blocker, octreotide); rarely transjugular intrahepatic portosystemic shunting

GI = gastrointestinal; PPI = proton pump inhibitor.

Evaluation

The initial step in evaluation is risk assessment to determine severity. This assessment includes measuring vital signs and reviewing patient factors. Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are associated with increased risk for rebleeding and death. Several clinical scores (e.g., the Glasgow-Blatchford and Rockall scores) are available to help predict risk for recurrent bleeding and mortality.

Findings of stigmata of chronic liver disease suggest a possible variceal source of bleeding.

Management

Hemodynamic status should be assessed in all patients, and resuscitative measures must be initiated with the goal of hemodynamic stabilization before endoscopy. Adequate intravenous access, usually with two large-bore peripheral intravenous catheters (minimum 18-gauge), should be established. Hemoglobin levels should be measured in all patients. A restrictive transfusion strategy is recommended and initiated when the hemoglobin level is below 7 g/dL (70 g/L) in hemodynamically stable patients without preexisting cardiovascular disease. Patients with hypotension due to severe, ongoing UGIB and those with concomitant cardiovascular disease should be considered for transfusion before the hemoglobin level decreases below 7 g/dL (70 g/L) to prevent the decreases below 7 g/dL (70 g/L) that may occur with fluid resuscitation alone. Care should be taken in patients with variceal hemorrhage because overtransfusion can precipitate variceal rebleeding due to increased portal pressure. Patients with altered mental status, massive hematemesis, or increased risk for aspiration should be considered for endotracheal intubation.

Pre-Endoscopic Care

Intravenous erythromycin given before endoscopy improves gastric visualization and decreases the need for repeat endoscopy, but it should be administered only when requested by the endoscopist. Nasogastric tube lavage is not required because there is no evidence of clinical benefit.

Intravenous proton pump inhibitor (PPI) therapy initiated before endoscopy decreases high-risk endoscopic stigmata in peptic ulcer disease and may reduce the need for endoscopic therapy (**Figure 39** and **Figure 40**), but it does not influence outcomes, such as rebleeding or death.

Octreotide, a somatostatin analogue that decreases splanchnic blood flow and lowers portal pressure, should be initiated if variceal hemorrhage is suspected. Initiation of antibiotics, such as ceftriaxone or quinolone, at the time of hospitalization for gastrointestinal bleeding is recommended for all patients with cirrhosis. Nearly 50% of patients with cirrhosis who are hospitalized with UGIB have a bacterial infection, such as pneumonia and urinary tract infection, and antibiotics reduce the rates of rebleeding and death. Balloon tamponade may be necessary as a temporizing measure for management of variceal bleeding until more definitive interventions are available.

In patients receiving warfarin with significant hemorrhage, warfarin should be discontinued and anticoagulation reversed with prothrombin complex concentrate with vitamin K. Endoscopy, however, should not be delayed for anticoagulation reversal. In patients receiving direct oral anticoagulants, the anticoagulant should be discontinued on presentation,

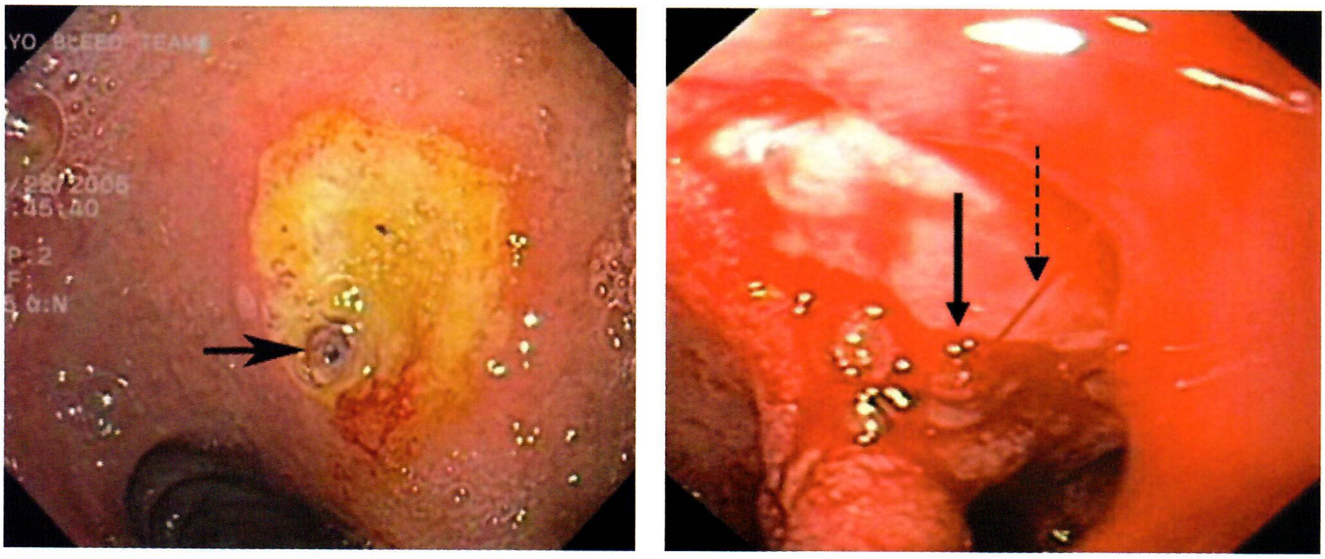

FIGURE 39. Duodenal ulcers. *Left*: Duodenal ulcer with nonbleeding visible vessel (*arrow*) that is at high risk for rebleeding and must be treated endoscopically. *Right*: Duodenal ulcer (*solid arrow*) with active arterial spurting (*dotted arrow*). This lesion is at the highest risk for rebleeding and must be treated endoscopically.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

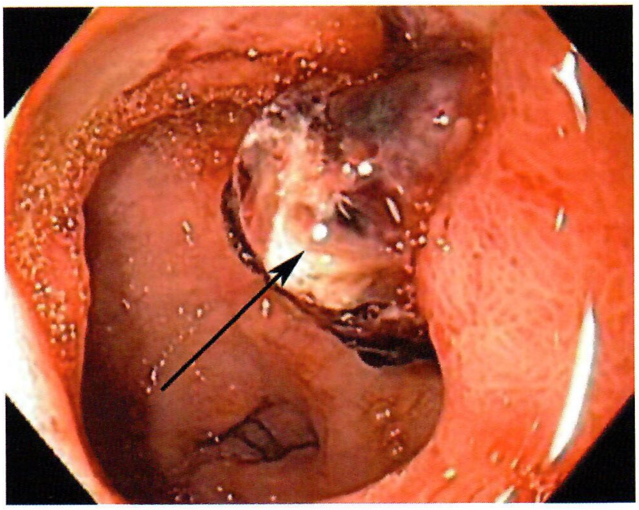

FIGURE 40. Duodenal ulcer with adherent clot (*arrow*) that is at risk for rebleeding. This can be treated medically or by clot removal and endoscopic therapy in addition to standard medical therapy.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

and, if significant hemorrhage is present, reversal with activated prothrombin complex concentrate or the appropriate agent (idarucizumab or andexanet alfa) should be considered. See MKSAP 19 Hematology for further information on reversal of anticoagulants.

In patients with active bleeding who have platelet counts less than 50,000/µL, platelets should be transfused. Aspirin for primary prevention of cardiovascular disease should be discontinued and not restarted because the risk for recurrent bleeding outweighs the benefit. Aspirin for secondary prevention in patients with high-risk cardiovascular disease should be discontinued only if necessary. Decisions about discontinuing dual antiplatelet therapy with a P2Y12 receptor antagonist and aspirin in patients with a recent acute coronary syndrome or coronary stent placement should be made with a cardiologist. In patients with significant hemorrhage in whom the P2Y12 receptor antagonist must be discontinued, aspirin should be continued.

Patients with hemodynamic instability, active bleeding (hematemesis or recurrent large-volume hematochezia), or suspected variceal hemorrhage should be admitted to an ICU. Most other patients can be admitted to a regular hospital ward. Several decision rules and predictive models have been developed to identify patients at low risk for recurrent or life-threatening UGIB. The modified Glasgow-Blatchford bleeding score is calculated using blood urea nitrogen level, hemoglobin level, systolic blood pressure, and pulse rate. It predicts the need for clinical intervention, rebleeding, and mortality. Patients at low risk with a modified Glasgow-Blatchford score of 1 or less may be considered for early discharge or outpatient treatment.

Endoscopic Evaluation and Treatment

Upper endoscopy is the primary diagnostic modality for evaluating UGIB. For patients hospitalized with UGIB, endoscopy should be performed within 24 hours of resuscitation; in those with rapid bleeding or suspected variceal hemorrhage, it should be done more emergently.

Endoscopy can determine the cause of bleeding and helps with risk stratification. Lesions at high risk for recurrent bleeding that require endoscopic treatment include actively bleeding peptic ulcers, ulcers with nonbleeding visible vessels (see Figure 39), and ulcers with adherent clots (see Figure 40). An adherent clot should be irrigated with the intention of removing the clot; the ulcer base is then examined to exclude an underlying arterial vessel requiring endoscopic hemostasis. Lesions at low risk for rebleeding (clean-based ulcers, ulcers with pigmented spots, and Mallory-Weiss tears) do not require endoscopic treatment (**Figure 41**). Most Mallory-Weiss tears

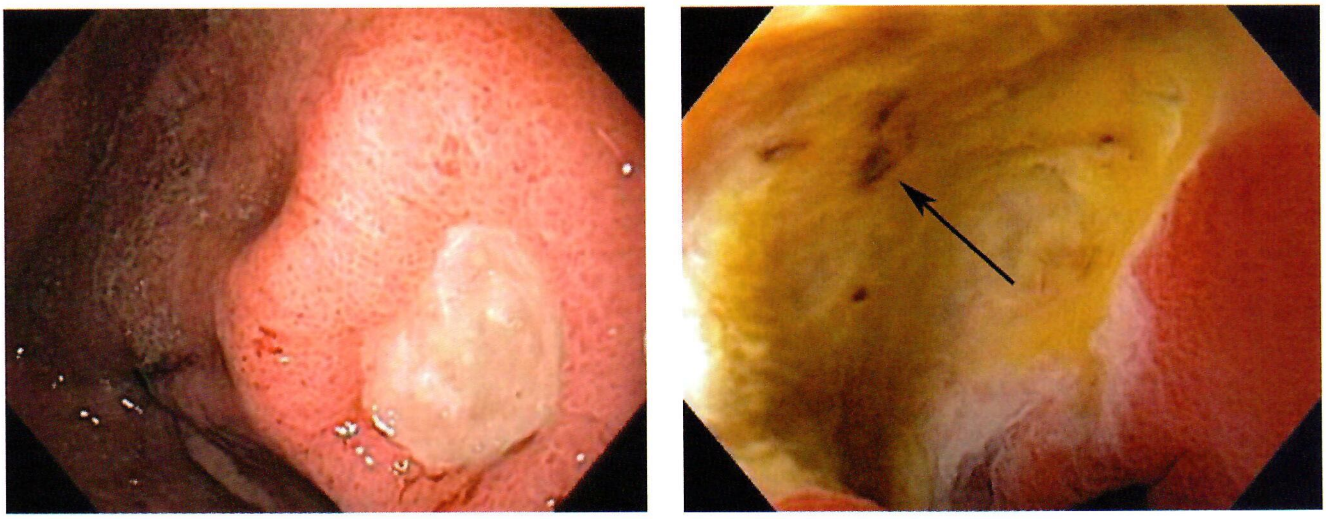

FIGURE 41. Ulcers at low risk for rebleeding, for which endoscopic therapy is not indicated. *Left:* Clean-based gastric ulcer with no blood vessels, pigmented spots/protuberances, or clots in the base. *Right:* Nonprotuberant pigmented spot (*arrow*) in a duodenal ulcer bed.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

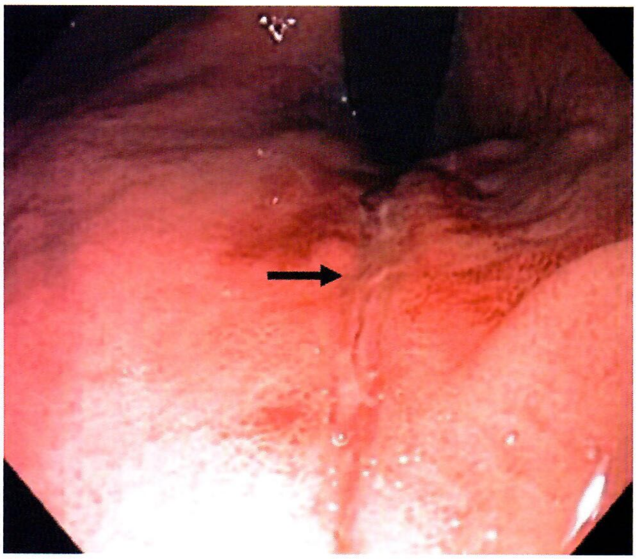

FIGURE 42. Mallory-Weiss tear. This superficial linear mucosal tear (*arrow*) is shown on endoscopic retroflexion in the proximal stomach.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

(**Figure 42**) stop bleeding spontaneously. Endoscopic techniques, such as injection therapy, thermal devices, and endoclips, can be used for actively bleeding tears.

The most effective approach for control of acute variceal hemorrhage (**Figure 43**) is combined therapy with octreotide and endoscopic therapy. Octreotide should be continued for 3 to 5 days after variceal hemorrhage. Endoscopic variceal ligation within 12 hours of presentation is the endoscopic treatment of choice for hemostasis of active variceal hemorrhage, with a success rate of 90%. In patients with bleeding gastric varices, endoscopic control may be difficult and transjugular intrahepatic portocaval shunting may be considered if bleeding persists despite octreotide.

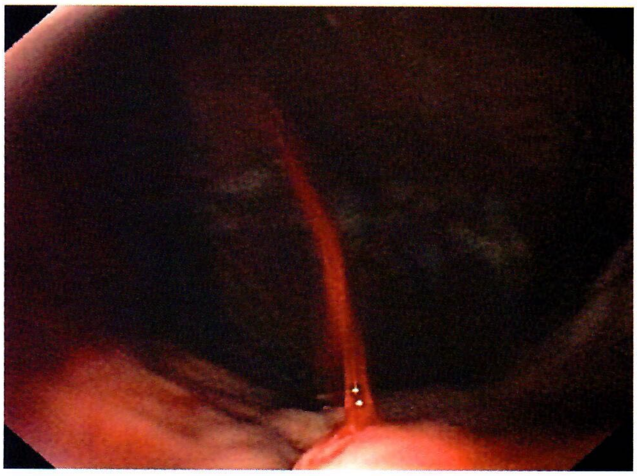

FIGURE 43. Acute esophageal variceal hemorrhage. A varix in the distal esophagus is seen spurting bright red blood.

The possibility of aortoenteric fistula should always be considered in patients who previously had aortic graft surgery and present with gastrointestinal bleeding because aortoenteric fistula is life-threatening, with a mortality rate of 50% even with surgical intervention. When there is a high degree of suspicion for an aortoenteric fistula, CT with intravenous contrast should be performed before endoscopy or other types of gastrointestinal evaluation.

Postendoscopic Care

Patients with peptic ulcer disease and low-risk stigmata can be fed within 24 hours of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital. Patients with high-risk lesions and those with adherent clots requiring endoscopic treatment should receive intravenous PPI therapy for 72 hours to decrease the risk for rebleeding and remain in the hospital for this interval. For high-risk lesions, twice-daily oral PPI therapy should continue for 2 weeks. Intermittent intravenous dosing is as efficacious as continuous infusion and may be preferable from a cost and logistic standpoint. For discussion of management of peptic ulcer disease, see Disorders of the Stomach and Duodenum.

Nonselective β-blocker therapy (propranolol, nadolol, or carvedilol) should be initiated in addition to endoscopic band ligation for secondary prophylaxis of variceal hemorrhage. The dosage of β-blockers should be increased as tolerated to obtain a resting pulse rate of 55 to 60/min. Subsequent endoscopy with further band ligation as needed to obliterate varices should also be performed every 2 to 4 weeks. Patients with cirrhosis and gastrointestinal bleeding should have antibiotic therapy continued for 7 days after hemorrhage, even in the absence of ascites.

Aspirin discontinued for secondary prevention of cardiovascular disease should be restarted as soon as possible after hemostasis is achieved. In patients with a recent acute coronary syndrome or coronary stent placement in whom a P2Y12 receptor was discontinued, therapy should be reinitiated within 5 days. In patients in whom warfarin was discontinued, re-anticoagulation with low-molecular-weight heparin or unfractionated heparin should be considered within 48 hours in patients at high thrombotic risk (mechanical prosthetic heart valve in the mitral position, atrial fibrillation with prosthetic heart valve or mitral stenosis, or recent venous thromboembolism). Timing of resuming direct oral anticoagulants depends on the risk profile, but resumption generally should occur within 7 days.

For all causes of UGIB, endoscopic therapy should be repeated if bleeding recurs, but routine second-look endoscopy is not recommended. Interventional radiology or surgery is reserved for cases of rebleeding despite endoscopic treatment. For variceal bleeding, placement of a transjugular intrahepatic portocaval shunt is reserved for bleeding that is not controlled by drug and endoscopic therapy.

KEY POINTS

- The most common causes of upper gastrointestinal bleeding include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear.
- Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are associated with increased risk for rebleeding and death in patients with upper gastrointestinal bleeding.
- Octreotide should be initiated if variceal hemorrhage is suspected, and initiation of antibiotics is recommended for all patients with cirrhosis.
- Endoscopic variceal ligation within 12 hours of presentation is the endoscopic treatment of choice for hemostasis of active variceal hemorrhage.
- HVC Patients with peptic ulcer disease and low-risk stigmata can be fed within 24 hours of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital.
- Patients with high-risk peptic ulcer lesions and those with adherent clots requiring endoscopic treatment should receive intravenous PPI therapy for 72 hours.

Lower Gastrointestinal Bleeding

Twenty percent of all cases of gastrointestinal bleeding originate in the colon or rectum. Most cases of LGIB stop spontaneously and have good outcomes; however, morbidity and mortality are higher in older patients and those with comorbid conditions. Patients with LGIB usually present with sudden onset of hematochezia (maroon or red blood per rectum). Occasionally, bleeding from the cecum or right colon may appear black and tarry, like melena. LGIB may also present with pain, diarrhea, or change in bowel movements.

Causes

The most common cause of minor LGIB is hemorrhoidal bleeding. This is usually characterized by a small volume of bright red blood and usually does not cause hemodynamic instability or significant volume loss (see Disorders of the Small and Large Bowel for discussion of hemorrhoids). Causes of severe LGIB that may lead to clinical instability include diverticular bleeding, colonic angiodysplasia, postpolypectomy bleeding, Dieulafoy lesion, rectal varices, and malignancy (**Table 42**). Fifteen percent of patients with hematochezia, however, are found to have an upper gastrointestinal source.

TABLE 42. Causes of Severe Lower Gastrointestinal Bleeding

Bleeding Source	Pathogenesis	Presentation	Treatment
Diverticulosis	Segmental weakness of arteries coursing over the dome of the diverticulum	Painless hematochezia or self-limited massive bleeding	Endoscopic, interventional radiologic, and surgical
Aortoenteric fistula	Erosion of aortic aneurysm (primary) into GI tract or following surgical or endovascular grafting (secondary)	Minor hemorrhage (herald bleeding) or massive bleeding	Aggressive resuscitation and emergent surgical repair
Rectal varices	Portal hypertension	Episodic hematochezia or severe bleeding (rare)	Endoscopic therapy and treatment of portal hypertension
Dieulafoy lesion	Erosion of an aberrant dilated submucosal blood vessel	Recurrent hematochezia or massive bleeding	Endoscopic therapy
Neoplasm	Tumor invasion	Recurrent episodes of hematochezia or melena or iron deficiency	Radiographic or endoscopic techniques or surgery
Colonic ischemia	Colonic hypoperfusion	Abdominal pain and hematochezia	Supportive care; surgical intervention for cases of irreversible ischemia
Inflammatory bowel disease	Mucosal inflammation and ulceration	Bloody diarrhea and abdominal pain	Medical therapy for underlying disease
Infectious colitis	Mucosal invasion of infectious organism	Bloody diarrhea	Treatment of causative organism
Intussusception	Intestinal wall ischemia from underlying obstruction	Hematochezia in setting of bowel obstruction	Surgical
Meckel diverticulum	Ulceration of small bowel from ectopic gastric mucosa-produced acid	Chronic and insidious bleeding or acute massive bleeding	Surgical resection of the diverticulum
Angiodysplasia	Ectatic, dilated, thin-walled blood vessels	Chronic and insidious bleeding or acute and massive bleeding	Endoscopic; interventional radiography and surgery in refractory cases

Diverticular bleeding is arterial and stops spontaneously in 75% of cases. In patients with diverticulosis, risk for bleeding is estimated at 0.5 per 1000 person-years. For further discussion of diverticular disease, see Disorders of the Small and Large Bowel.

Angiodysplasia, also known as angiectasia or arteriovenous malformation, can occur throughout the colon but is most common in the right colon. Elderly patients, patients with end-stage kidney disease, and patients receiving anticoagulation therapy are at highest risk. Patients with cardiac disease, especially valve dysfunction, and patients with left ventricular assist devices may be at increased risk for gastrointestinal bleeding secondary to acquired von Willebrand disease.

Postpolypectomy bleeding can occur immediately after polyp removal or days or weeks later. Risk is increased in patients with polyps larger than 2 cm or polyps in the right colon and with resumption of antithrombotic therapy.

Diarrhea, abdominal pain, and hematochezia can occur with inflammatory bowel disease and infectious colitis; ischemic colitis may also present with these symptoms, although the bleeding is rarely significant. LGIB from a colon malignancy may be painless or associated with obstructive symptoms.

Evaluation

An initial patient assessment and hemodynamic resuscitation should be performed simultaneously. The timing and quality of any previous colonoscopy should be assessed, particularly for a report of polypectomy or biopsies. A careful assessment should be performed for use of antithrombotic or antiplatelet agents as well as for a personal history of or risk factors for liver disease, other comorbidities, or recent illness. Special attention should be paid to the factors that suggest an upper gastrointestinal source of hematochezia, including concomitant melena, liver disease, and hemodynamic instability.

Management

As with upper gastrointestinal bleeding, immediate attention should be paid to hemodynamic status, and resuscitative measures must be initiated with the goal of hemodynamic stabilization before endoscopy. The approach to management of hemoglobin level and platelet count are as described for UGIB, as are decisions regarding discontinuation and/or reversal of anticoagulant and antiplatelet agents.

CT angiography is the initial diagnostic test in patients who are hemodynamically unstable after initial resuscitation or have rapid ongoing bleeding, followed by immediate upper endoscopy if CT angiography does not reveal a source of bleeding. Upper endoscopy may also be a reasonable first choice in patients at risk for a rapidly bleeding upper gastrointestinal source for hematochezia.

In hemodynamically stable patients without evidence of rapid bleeding, colonoscopy is the first study of choice in patients with LGIB. It should be performed within 24 hours of presentation after adequate colon preparation, which may include rapid preparation. Colonoscopy identifies a source of LGIB in two thirds of patients.

Radiographic studies should be considered in patients who cannot tolerate colonoscopy or colon preparation or in patients in whom a source of bleeding is not identified endoscopically. Techniques include CT angiography, angiography, and, less frequently, tagged red blood cell scintigraphy.

Catheter-based angiography with embolization should be performed as soon as possible if active bleeding is noted on CT angiography. Angiographic embolization is also frequently used to stop persistent or recurrent diverticular bleeding because of the limitations of endoscopic approaches. Surgical consultation is reserved for patients who do not respond to endoscopic or interventional radiologic hemostatic measures.

The risk for rebleeding is highest in patients with diverticular bleeding (9% to 47%) and angiodysplasia bleeding (37% to 64%). To prevent recurrent LGIB, nonaspirin NSAIDs should be avoided, particularly after diverticular or angiodysplasia bleeding. Management of antiplatelet and anticoagulant medications is similar to that in patients with UGIB.

KEY POINTS

- CT angiography is the initial diagnostic test in patients who have lower gastrointestinal bleeding, are hemodynamically unstable, or have rapid ongoing bleeding, followed by immediate upper endoscopy if CT angiography does not reveal a source of bleeding.
- Catheter-based angiography with embolization should be performed as soon as possible if active bleeding is noted on CT angiography.
- In hemodynamically stable patients with lower gastrointestinal bleeding but no evidence of rapid bleeding, colonoscopy is the first study of choice and should be performed within 24 hours of presentation.

Small-Bowel Bleeding

Small-bowel bleeding occurs secondary to a gastrointestinal bleeding source between the ampulla of Vater and ileocecal valve. It can be overt, in which visible bleeding (melena or hematochezia) is present, or occult, which is characterized by anemia in the absence of gross signs of bleeding. Roughly 5% to 10% of gastrointestinal bleeding is due to a small-bowel source.

Causes

The causes of small-bowel bleeding vary with patient age (**Table 43**). Angiodysplasia (**Figure 44**) is the most common cause. Patients younger than 40 years are likely to have small-bowel bleeding due to inflammatory bowel disease, Dieulafoy lesions, neoplasia, Meckel diverticulum, or a polyposis syndrome. Patients age 40 years and older are likely to have bleeding due to angiodysplasia, Dieulafoy lesions, neoplasia, or NSAID-related ulcers. Rare causes include Henoch-Schönlein purpura, small-bowel varices or portal hypertensive enteropathy, amyloidosis, blue rubber bleb nevus syndrome, aortoenteric fistula, and radiation enteritis.

TABLE 43. Causes of Small-Bowel Gastrointestinal Bleeding

Differential Diagnosis	Patient Age (y)	Clinical Clues
Angiodysplasia	>60	Intermittent, usually occult bleeding; may also occur in colon
Peutz-Jeghers syndrome	<20	Perioral pigmentation; obstructive symptoms
Meckel diverticulum	20-60	Possible abdominal pain
Hemangioma	<20	Possible cutaneous hemangiomas
Malignancy	>50	Weight loss; abdominal pain
Hereditary hemorrhagic telangiectasia	>50	Mucocutaneous telangiectasias

Evaluation

Important elements of the history include assessment for NSAID use; inflammatory bowel disease; prior aortic aneurysm repair; prior pancreatitis; and recent liver trauma, tumor, or biopsy. Key physical findings may include perioral pigmentation or mucocutaneous or cutaneous telangiectasia (**Figure 45**).

If a bleeding source is not identified on initial endoscopy and colonoscopy and small-bowel bleeding is suspected, second-look upper endoscopy or colonoscopy should be done if the initial studies were low quality or other clinical factors exist, because missed lesions on the initial endoscopy are common (**Table 44**). Push enteroscopy may be pursued in lieu of endoscopy to visualize the distal duodenum and proximal jejunum. Repeat colonoscopy should include intubation of the terminal ileum.

Stable Patients

For evaluating stable patients suspected of having small-bowel bleeding, video capsule endoscopy is the preferred test after nondiagnostic upper endoscopy and colonoscopy, with a diagnostic yield of 56% to 67%. This test uses a nondigestible wireless capsule camera (**Figure 46**) that is swallowed or placed endoscopically. Limitations include the inability to intervene therapeutically and precisely localize a lesion; lesions may also be missed. The primary complication is capsule retention due to obstruction or stricture. For suspected obstruction or altered anatomy (small-bowel Crohn disease, radiation enteritis, prior small-bowel surgery), CT enterography or magnetic resonance enterography should be performed instead. Barium-based

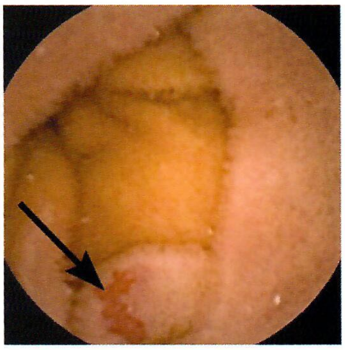

FIGURE 44. Capsule endoscopy image of angiodysplasia. This red lesion (*arrow*) has a fernlike pattern.

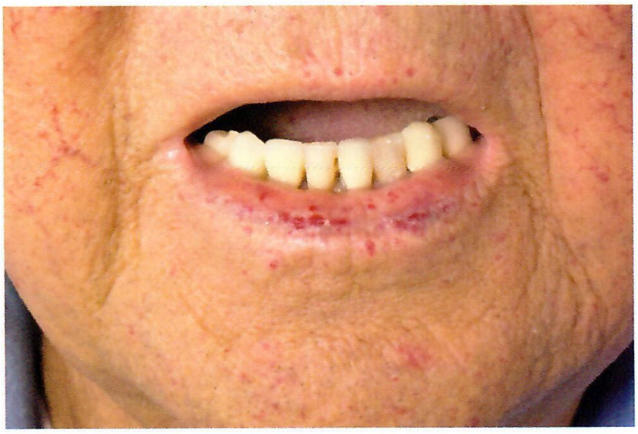

FIGURE 45. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is a disorder of development of the vasculature characterized by telangiectases and arteriovenous malformations in specific locations. The most common features of the disorder–nosebleeds and telangiectases on the lips, hands, and oral mucosa–are often subtle.

TABLE 44. Clinical Factors Suggesting Need for Second-Look Endoscopy, Push Enteroscopy, or Colonoscopy in Suspected Small-Bowel Bleeding

Fresh blood or clot on initial upper endoscopy and/or colonoscopy limiting visualization
Large hiatal hernia
History of NSAID use
Poor colon preparation for initial colonoscopy
Incomplete colonoscopy

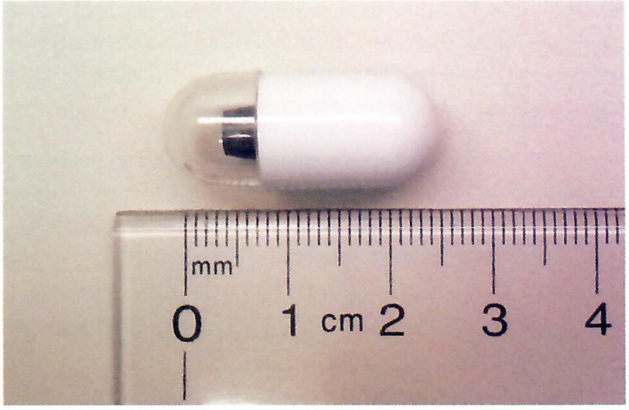

FIGURE 46. Endoscopy capsule.

Courtesy of Elizabeth Rajan, MD, Mayo Clinic.

studies are no longer recommended for suspected small-bowel bleeding given their poor diagnostic yield (3%-6%).

Hemodynamically Unstable Patients

As in LGIB, CT angiography is the diagnostic test of choice for hemodynamically unstable patients or for those with brisk small-bowel bleeding. It is widely available, provides rapid testing, and has good diagnostic accuracy (sensitivity, 89%; specificity, 85%). In patients with contraindications to CT, technetium-99m-labeled red blood cell or sulfur colloid nuclear scanning may be considered. The primary weakness of radioisotope-labeled scanning is the propensity to poorly localize the bleeding site.

Management

After hemodynamic stabilization, therapy is guided by the source and location of bleeding. For active bleeding identified by CT angiography or red blood cell scanning, angiography with embolization should be performed. When a bleeding source is identified on video capsule endoscopy or CT angiography, device-assisted enteroscopy (single-balloon system, double-balloon system, or spiral enteroscopy) or push enteroscopy should be performed with one or more endoscopic methods of hemostasis. Intraoperative endoscopy during laparotomy/laparoscopy is the most invasive modality and is a last resort.

Pharmacologic therapy is possible for some underlying etiologies but is reserved for patients with contraindications to or no response to endoscopic or interventional radiologic intervention. The somatostatin analogue octreotide and the anti-angiogenesis agent thalidomide have potential efficacy for vascular lesions. Hormonal therapy no longer has a role because of poor efficacy.

Tumors or masses require surgical intervention, and, if massive bleeding is present, embolization of the bleeding vessel may be necessary.

Anemia should be treated with blood transfusion when the hemoglobin level is below 7 g/dL (70 g/L) in hemodynamically stable patients without preexisting cardiovascular disease and iron supplementation thereafter if iron deficiency is found. If a causative agent is identified, such as an NSAID, the agent should be stopped. Patients with angiodysplasia and associated aortic stenosis (Heyde syndrome) benefit from valve replacement surgery if indicated from a cardiac standpoint.

KEY POINTS

- If small-bowel bleeding is suspected, second-look upper endoscopy and colonoscopy or push enteroscopy should be considered before small-bowel evaluation, especially if previous endoscopic studies were low quality.
- Video capsule endoscopy is preferred for evaluating stable patients for small-bowel bleeding following nondiagnostic endoscopy and colonoscopy.
- CT angiography is the diagnostic test of choice for hemodynamically unstable patients or for those with brisk small-bowel bleeding.

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Gastroenterology and Hepatology Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Physicians designates MKSAP 19 Gastroenterology and Hepatology for a maximum of 24 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 24 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Earn Credits or MOC Points Online

To earn CME credits or to apply for MOC points, MKSAP users need to answer at least one of two questions correctly (earning a score of at least 50%) and click the Submit CME button. Each single MKSAP 19 self-assessment question qualifies for one quarter of a CME credit hour or ABIM MOC point.

MKSAP 19 Subscribers can enter their self-assessment question answers and submit for CME/MOC in two ways:

1. Users of MKSAP 19 Complete who prefer to use their print books and a paper answer sheet to study and record their answers can use the printed answer sheet at the back of this book to record their answers. The corresponding online answer sheets, which are available on the MKSAP 19 Resource Page, may be used to transcribe answers onto the online answer sheets. Users may then submit their answers to qualify for CME credits or MOC points (see below for information on Opting in for MOC). Users who prefer to record their answers on a paper answer sheet should save their answer sheet for future use. Users who study with MKSAP 19 print can also submit their answers directly within MKSAP 19 Digital by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions.
2. Users of MKSAP 19 Digital can enter their answers within the digital program by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions and clicking the Submit CME button once they qualify for CME and are ready to submit. Learners should keep in mind their yearly CME and MOC deadlines when determining the appropriate time to submit.

Learners' CME/MOC submission progress will be shown on the MKSAP 19 Digital CME/MOC/CPD page.

Opting in for MOC

MKSAP 19 users can opt in for simultaneous submission of CME and MOC points as they answer self-assessment questions. To opt in, users will be required to complete a form requesting their name, date of birth, and ABIM number. The MOC Opt-in Form will be presented upon the user's first CME submission and needs to be completed only once.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 74-year-old woman is evaluated in the emergency department for yellow skin, dark urine, and light stools of 10 days' duration.

On physical examination, vital signs are normal. Jaundice and icteric sclerae are noted.

Laboratory studies:

Alkaline phosphatase	175 U/L
Alanine aminotransferase	57 U/L
Aspartate aminotransferase	49 U/L
Total bilirubin	6.0 mg/dL (102.6 µmol/L)
Direct bilirubin	4.6 mg/dL (78.7 µmol/L)

CT reveals retroperitoneal fibrosis and a "sausage-shaped" pancreas with a narrowed pancreatic duct. Endoscopic ultrasound with fine-needle aspiration is negative for malignancy but shows more than 10 IgG4-positive cells/hpf.

Which of the following is the most appropriate management?

(A) Azathioprine
(B) Endoscopic retrograde cholangiopancreatography with biliary stent placement
(C) Prednisone
(D) Total pancreatectomy

Item 2

A 45-year-old woman is evaluated at follow-up for abnormal alkaline phosphatase levels on three previous blood tests. She has mild pruritus. She has no family history of liver disease. She has no other medical concerns and does not take any medications.

Vital signs and other physical examination findings are normal.

Her complete blood count and alanine aminotransferase, aspartate aminotransferase, serum albumin, serum total bilirubin, and total protein are within normal limits. The alkaline phosphatase level is 212 U/L.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Antimitochondrial antibody
(B) Anti-smooth muscle antibody
(C) Liver biopsy
(D) Serum IgG4

Item 3

A 50-year-old man is evaluated for newly developed ascites. He has cirrhosis due to nonalcoholic steatohepatitis. Paracentesis confirms cirrhosis as a cause of the ascites and excludes infection, and a low-sodium diet is implemented. Medical history includes type 2 diabetes mellitus, hypertension, and dyslipidemia. Current medications are metformin, lisinopril, and atorvastatin.

On physical examination, vital signs are normal. The abdomen is nontender and mildly distended, with normal bowel sounds.

Serum creatinine level is 1.1 mg/dL (97.2 µmol/L). Random urine protein-creatinine ratio is 16 mg/g.

Which of the following is the most appropriate additional treatment?

(A) Discontinue atorvastatin
(B) Discontinue lisinopril
(C) Initiate lactulose
(D) Initiate low-protein diet

Item 4

A 30-year-old woman is evaluated at a new-patient visit. She was born in Somalia and immigrated to the United States 2 years ago.

On physical examination, vital signs and other findings are normal.

Laboratory studies:

Alanine aminotransferase	24 U/L
Hepatitis B virus DNA	Undetected
Hepatitis B core antigen IgG antibody	Positive
Hepatitis B surface antibody	Negative
Hepatitis B surface antigen	Positive
Hepatitis E antigen	Negative
Hepatitis E IgG antibody	Positive

Which of the following best describes this patient's phase of hepatitis B virus infection?

(A) Immune active
(B) Immune control
(C) Immune tolerant
(D) Reactivation

Item 5

A 52-year-old man is evaluated in the emergency department because of a 6-day history of fatigue, malaise, fever, and abdominal pain. He has not recently traveled. Five weeks ago, he had a 1-week episode of low-grade fever and left-lower-quadrant abdominal pain that resolved spontaneously.

On physical examination, temperature is 38.2 °C (100.9 °F), blood pressure is 110/80 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. The right upper quadrant of the abdomen is tender to palpation. The remainder of the examination is normal.

Laboratory studies:

Leukocyte count	17,000/µL (17×10^9/L)
Alkaline phosphatase	220 U/L
Alanine aminotransferase	65 U/L
Aspartate aminotransferase	55 U/L

Ultrasound demonstrates a 3.5-cm hypoechoic, fluid-filled mass in the right side of the liver.

Empiric treatment with ceftriaxone plus metronidazole is initiated.

Which of the following is the most appropriate additional treatment?

(A) Needle aspiration
(B) Percutaneous drain
(C) Surgical resection
(D) No additional treatment is necessary

Item 6

A 65-year-old woman is evaluated in the emergency department for a 2-day history of left-lower-quadrant abdominal pain and constipation. She reports having had nausea for 1 day but no vomiting. She has hypertension and type 2 diabetes mellitus and underwent renal transplantation 2 years ago. Current medications are prednisone, mycophenolate mofetil, enalapril, and insulin.

On physical examination, temperature is 37.8 °C (100.1 °F); other vital signs are normal. Abdominal examination reveals left-lower-quadrant tenderness, with no guarding or mass.

Laboratory studies:

Hemoglobin	13 g/dL (130 g/L)
Leukocyte count	11,000/µL (11×10^9/L), with 70% polymorphonuclear cells
Blood urea nitrogen	22 mg/dL (7.9 mmol/L)
Creatinine	1.2 mg/dL (106.1 µmol/L)

Contrast-enhanced CT scans of the abdomen and pelvis show diverticula in the sigmoid colon with bowel wall thickening and pericolonic mesenteric fat stranding. There is no abscess, obstruction, or fistula.

Which of the following is the most appropriate management?

(A) Colonoscopy now
(B) Discharge to home with oral antibiotics
(C) Hospitalization for intravenous antibiotics
(D) Surgery

Item 7

A 43-year-old woman is evaluated in the emergency department for confusion and a 1-week history of yellow skin. She consumes 12 beers daily.

On physical examination, temperature is 38.5 °C (101.3 °F); blood pressure is 120/50 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. Her sclerae are icteric and skin is jaundiced. Tender hepatomegaly is present. She has asterixis and is oriented to person only. No source of infection has been identified. Maddrey discriminant function score is 35.

Laboratory studies:

Leukocyte count	14,000/µL (14×10^9/L)
Prothrombin time	14.0 s (control, 10.0 s)
Alkaline phosphatase	200 U/L
Alanine aminotransferase	30 U/L
Aspartate aminotransferase	62 U/L
Total bilirubin	17.0 mg/dL (290.7 µmol/L)

Ultrasound of the right upper quadrant shows hepatomegaly, minimal ascites, liver echogenicity, and no biliary stones or ductal dilation.

Which of the following is the most appropriate management?

(A) Cefepime
(B) Liver biopsy
(C) Pentoxifylline
(D) Prednisolone

Item 8

A 60-year-old woman is evaluated for follow-up after screening colonoscopy. Colonoscopy revealed a 7-mm sessile serrated polyp, which was completely removed. Three 2-mm hyperplastic polyps were removed from the rectum. She is asymptomatic and has no other medical conditions. Family history is negative for colon cancer. She takes no medications.

Which of the following is the most appropriate surveillance approach?

(A) Colonoscopy in 1 year
(B) Colonoscopy in 5 to 10 years
(C) Fecal DNA-based testing in 3 years
(D) Fecal occult blood testing annually

Item 9

A 44-year-old woman is evaluated for a 3-month history of irregular bowel habits, characterized by four or five episodes of watery, nonbloody watery diarrhea daily for 2 to 3 days every 3 to 4 weeks. She has lost 2.3 kg (5.1 lb) during the past 3 months. She also has osteoporosis treated with calcium, vitamin D, and alendronate. Her sister has celiac disease.

On physical examination, vital signs and other findings are normal. BMI is 21.

Laboratory evaluation reveals a total IgA level less than 500 mg/dL (5 g/L), tissue transglutaminase IgA level of 0 U/mL (normal, 0-3 U/mL), and IgG level of 800 mg/dL (8 g/L).

Which of the following is the most appropriate management?

(A) Anti-deamidated gliadin peptide IgG antibody measurement
(B) Anti-gliadin IgA and IgG antibody measurement
(C) Gluten-free diet
(D) *HLA-DQ2* and *HLA-DQ8* testing

Item 10

A 36-year-old woman is evaluated for a 3-day history of constant right-upper-quadrant abdominal discomfort and abdominal distention. She has no significant medical history. Her only medication is a combined oral contraceptive pill.

On physical examination, vital signs are normal. Palpation reveals a tender, enlarged liver. Ascites is present. Bowel sounds are normal.

Laboratory evaluation shows an alanine aminotransferase level of 152 U/L and aspartate aminotransferase level of 138 U/L.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal Doppler ultrasonography
(B) Abdominal radiography
(C) Hepatobiliary iminodiacetic acid scintigraphy
(D) Noncontrast abdominal CT

Item 11

A 22-year-old man is evaluated in the office for hepatitis A virus (HAV) exposure that occurred 5 days ago. The source of exposure is the patient's college roommate, who is now at home recovering from the illness. The patient's mother has confirmed he has never been vaccinated against HAV.

On physical examination, vital signs and other findings are normal.

Which of the following is the most appropriate preventive measure?

(A) Hepatitis A virus vaccine
(B) HAV immune globulin
(C) HAV vaccine and HAV immune globulin
(D) No preventive measures

Item 12

A 40-year-old man is evaluated in the emergency department for severe epigastric abdominal pain radiating to the back that has worsened in the past 12 hours.

On physical examination, temperature is 39.4 °C (102.9 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 28/min. Palpation of abdomen elicits epigastric pain without guarding.

Laboratory studies:

Leukocyte count	18,000/µL (18×10^9/L)
Alanine aminotransferase	178 U/L
Aspartate aminotransferase	145 U/L
Total bilirubin	1.1 mg/dL (18.8 µmol/L)
Lipase	100 U/L

Blood and urine cultures are pending.

Fluid resuscitation with lactated Ringer solution is initiated.

Which of the following is the most appropriate initial management?

(A) Contrast-enhanced CT
(B) Empiric antibiotics
(C) Endoscopic ultrasonography
(D) Triglyceride measurement

Item 13

A 22-year-old woman is evaluated in the emergency department for an episode of confusion, diaphoresis, and tremulousness. Similar symptoms have been present for 6 months but are becoming more frequent and severe.

Fingerstick blood glucose level is 30 mg/dL (1.7 mmol/L). Her symptoms resolve with administration of glucose. Subsequent evaluation reveals an elevated C-peptide level, a plasma glucose level of 45 mg/dL (2.5 mmol/L), and an elevated fasting insulin level.

A contrast-enhanced multidetector CT scan shows a highly vascular mass consistent in appearance with a pancreatic neuroendocrine tumor.

Genetic testing for which of the following should be included in this patient's evaluation?

(A) Multiple endocrine neoplasia type 1
(B) Multiple endocrine neoplasia type 2
(C) Neurofibromatosis type 1
(D) Tuberous sclerosis

Item 14

A 52-year-old man is evaluated for a 6-month history of constipation. He has bowel movements once every 5 days, low back pain after 2 days without a bowel movement, and straining during defecation. He reports no abdominal pain. Colon cancer screening was performed 2 years ago with fecal immunochemical testing.

On physical examination, vital signs are normal. Abdominal examination reveals palpable stool in the left lower quadrant without tenderness. Result of digital anorectal examination is normal.

Laboratory studies show a hematocrit of 44%.

Which of the following is the most appropriate management?

(A) Colonoscopy
(B) Prucalopride
(C) Psyllium
(D) Radiopaque marker study

Item 15

A 34-year-old woman is evaluated at routine follow-up after diagnosis of primary sclerosing cholangitis (PSC) earlier this month. The diagnosis of PSC was confirmed with magnetic resonance cholangiopancreatography showing multifocal intra- and extrahepatic bile duct strictures without evidence of a dominant stricture or mass. A carbohydrate antigen 19-9 measurement was normal. She has no other medical conditions and takes no medications.

Which of the following is the most appropriate management at this time?

(A) Colonoscopy
(B) Endoscopic retrograde cholangiopancreatography
(C) Liver biopsy
(D) Liver transplantation

H

Item 16

A 65-year-old woman is hospitalized for acute pancreatitis due to alcohol use. During hospitalization, she receives lactated Ringer solution overnight and is taking nothing by mouth.

On physical examination the morning after admission, the patient reports improved pain. Vital signs are normal. She has mild epigastric pain without guarding. Bowel sounds are present.

After fluid resuscitation, hematocrit decreases from 45% at admission to 38% 12 hours later.

Which of the following is the most appropriate management?

(A) Initiate enteral tube feeding
(B) Initiate oral feeding
(C) Maintain nothing-by-mouth status
(D) Transfuse 2 units of packed red blood cells

Item 17

A 55-year-old man is evaluated for gastroesophageal reflux disease (GERD). He has a 20-year history of GERD, which is well controlled with medication. He is an active cigarette smoker with a 30-pack-year history. He does not drink alcohol. A chest radiograph obtained 2 years ago for the evaluation of fever and cough revealed a hiatal hernia. His only medication is omeprazole.

On physical examination, vital signs are normal. BMI is 37. Other than abdominal obesity, the physical examination is normal.

Which of the following is the most appropriate initial management?

(A) Bariatric surgery
(B) Esophageal motility study
(C) Fundoplication
(D) Upper endoscopy

Item 18

A 47-year-old woman is evaluated at a follow-up appointment. Autoimmune hepatitis was diagnosed 1 year ago when she developed jaundice. Current medications are prednisone and azathioprine. Her liver enzyme levels have been normal for 9 months, and her jaundice has resolved.

Vital signs and other physical examination findings are normal.

Which of the following is the most appropriate management?

(A) Continue immunosuppressant therapy
(B) Perform liver biopsy now
(C) Stop azathioprine and taper prednisone
(D) Stop azathioprine, taper prednisone, and perform liver biopsy

Item 19

H

A 68-year-old woman is evaluated in the emergency department for sudden-onset, crampy, left-lower-quadrant abdominal pain followed several hours later by passage of bright red blood per rectum. She has hypertension and hyperlipidemia. Current medications are lisinopril and simvastatin.

On physical examination, vital signs are normal. Abdomen is soft and nondistended, with left-lower-quadrant tenderness and no rebound or guarding. Anorectal examination shows scant bright red blood in the rectal vault.

Laboratory testing shows a leukocyte count of 12,000/µL (12×10^9/L) and a blood urea nitrogen level of 24 mg/dL (8.5 mmol/L); other routine laboratory results are normal.

Abdominal and pelvic CT scan shows only segmental thickening of the descending and sigmoid colon.

Which of the following is the most likely diagnosis?

(A) Acute diverticulitis
(B) *Clostridioides difficile* infection
(C) Colonic ischemia
(D) Ulcerative colitis

Item 20

A 20-year-old woman is evaluated for loose, bloody stools up to three times daily with prominent fecal urgency. She has no other symptoms.

On physical examination, all vital signs are normal. Abdominal examination is normal. Anorectal examination elicits mild discomfort.

Laboratory evaluation shows a normal complete blood count and liver chemistries. Results of testing for *Clostridioides difficile* toxin are negative.

Colonoscopy shows moderate inflammatory mucosal changes involving the rectum in a diffuse, continuous fashion, characterized by edema, erythema, and erosions. Abrupt transition to normal-appearing mucosa in the upper rectum is evident, and the remaining colonic mucosa above the rectum is normal. Biopsy specimens from the rectum reveal moderate chronic colitis with crypt architectural distortion.

Which of the following is the most appropriate treatment?

(A) 5-Aminosalicylate suppository
(B) Glucocorticoid suppository
(C) Oral 5-aminosalicylate
(D) Oral glucocorticoid

Item 21

A 42-year-old man is evaluated after screening laboratory tests obtained before initiation of statin therapy revealed isolated elevated aminotransferase levels. He is asymptomatic. His only active medical condition is type 2 diabetes mellitus. Medications are metformin and moderate-intensity atorvastatin.

On physical examination, vital signs and other findings are normal. Waist circumference is normal. BMI is 23.

Laboratory studies:

Hemoglobin	18 g/dL (180 g/L)
Alanine aminotransferase	43 U/L
Aspartate aminotransferase	56 U/L
Ferritin	1200 ng/mL (1200 μg/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) α_1-Antitrypsin antibody measurement
(B) Liver biopsy
(C) Transferrin saturation measurement
(D) Urine porphyrin measurement

Item 22

A 25-year-old woman is evaluated for watery, nonbloody diarrhea of 9 months' duration, occurring four times daily but not nocturnally. It is usually accompanied by abdominal pain in the periumbilical area or left lower quadrant. Pain usually diminishes after a bowel movement. She has had no weight loss.

On physical examination, vital signs are normal. BMI is 22. Abdominal examination reveals minimal tenderness in the left lower quadrant.

Laboratory studies show normal fecal calprotectin, thyroid-stimulating hormone, hematocrit, tissue transglutaminase IgA, and liver chemistries. The test result for *Clostridioides difficile* is negative.

Which of the following is the most appropriate diagnostic test?

(A) Abdominal ultrasonography
(B) Colonoscopy with biopsy of right and left colon
(C) Stool testing for *Escherichia coli* O157:H7
(D) Stool testing for *Giardia*

Item 23

A 70-year-old man is hospitalized for a 12-hour history of painless intermittent maroon stools (four episodes). One hour ago he evacuated a large maroon stool. He has hypertension, coronary artery disease, and osteoarthritis. Current medications are metoprolol, atorvastatin, aspirin, acetaminophen, naproxen as needed, and omeprazole.

On physical examination, blood pressure is 90/50 mm Hg and pulse rate is 100/min. The abdomen is soft and nontender. Maroon stool is present around anus.

Hemoglobin level is 11 g/dL (110 g/L).

After a 500-mL infusion of 0.9% saline, blood pressure is 96/65 mm Hg and pulse rate is 105/min.

Bilious return is noted on gastric lavage after placement of a nasogastric tube.

Which of the following is the most appropriate next diagnostic test?

(A) Angiography
(B) Colonoscopy
(C) CT angiography
(D) Upper endoscopy

Item 24

A 62-year-old man is admitted to the ICU for hematemesis. He has a history of cirrhosis due to alcohol use. He undergoes hemodynamic stabilization and initiation of octreotide and antibiotics. Other current medications are propranolol, spironolactone, and furosemide.

On physical examination, blood pressure is 104/58 mm Hg, pulse rate is 62/min, and respiration rate is 16/min. Ascites is present. Bowel sounds are normal, and abdomen is not tender.

Endoscopy reveals large varices isolated to the gastric fundus, along the greater curvature of the stomach, that have stigmata of recent bleeding.

Which of the following is the most appropriate next step in management?

(A) Abdominal CT with contrast
(B) Abdominal ultrasonography
(C) Balloon tamponade
(D) Band ligation of varices

Item 25

A 21-year-old woman is evaluated at follow-up after upper endoscopy and colonoscopy, which were performed because of iron deficiency anemia unresponsive to oral iron therapy. Upper endoscopy revealed fundic gland polyps carpeting the stomach and multiple small adenomatous polyps in the duodenum. Colonoscopy demonstrated more than 100 polyps throughout the colon, with 2 polyps in the rectum. Biopsy of a 3-cm polyp in the sigmoid colon revealed moderately differentiated adenocarcinoma. The patient has no family history of colorectal cancer.

Which of the following is the most appropriate treatment?

(A) Colectomy
(B) Endoscopic removal of the adenocarcinoma
(C) Left hemicolectomy
(D) Sulindac

Item 26

A 50-year-old man is evaluated at a routine follow-up appointment. He has a history of cirrhosis due to hepatitis C virus (HCV) infection. He previously underwent successful antiviral therapy for HCV infection. He has never had symptoms referable to liver disease and feels well. He is not taking any medications.

On physical examination, vital signs are normal and other findings are unremarkable.

Laboratory studies:

Platelet count	155,000/μL (155×10^9/L)
INR	1.0
Albumin	3.4 g/dL (34 g/L)
Alanine aminotransferase	25 U/L
Aspartate aminotransferase	34 U/L
Total bilirubin	1.2 mg/dL (20.5 μmol/L)

Routine abdominal ultrasound screening and follow-up MRI show a 1.5-cm lesion in the left liver consistent with hepatocellular cancer. There is no evidence of metastatic disease.

Which of the following is the most appropriate management?

(A) Liver transplantation
(B) Surgical resection
(C) Transarterial chemoembolization
(D) Ongoing surveillance

Item 27

A 34-year-old man is evaluated at follow-up for abnormal liver chemistry test results. The abnormal results were detected 2 weeks ago, on the day of hospital admission for an ulcerative colitis flare. During hospitalization, he was treated with intravenous glucocorticoids. At the time of discharge, acute prostatitis was diagnosed and a 4-week course of levofloxacin was initiated.

Follow-up laboratory studies:	
Alkaline phosphatase	258 U/L
Alanine aminotransferase	39 U/L
Aspartate aminotransferase	42 U/L
Total bilirubin	1.0 mg/dL (17.1 µmol/L)

Magnetic resonance cholangiopancreatography shows normal bile ducts and gallbladder, with no gallbladder stones.

Which of the following is the most appropriate next step in management?

(A) Discontinuation of levofloxacin
(B) Endoscopic retrograde cholangiopancreatography
(C) Liver biopsy
(D) Liver ultrasonography

Item 28

A 33-year-old woman is evaluated during her annual follow-up visit. She is asymptomatic. She has a 2-year history of left-sided ulcerative colitis, now in remission. Current medications are an oral 5-aminosalicylate and azathioprine. All immunizations are up to date, and depression and anxiety screening results are negative. Skin cancer screening was performed 6 months ago. Her last cervical cancer screening was 1 year ago.

Which of the following is the most appropriate health maintenance screening test to perform?

(A) Anal cancer screening
(B) Cervical cancer screening
(C) Colonoscopy
(D) Dual-energy x-ray absorptiometry

Item 29

A 27-year-old man is evaluated in the emergency department for inability to eat, drink, or swallow his saliva for the past 2 hours. Symptoms began while he was eating chicken, when he felt that the bolus did not move all the way down his esophagus. During evaluation, he begins to sense that he can swallow again. He has had several previous but less severe episodes of dysphagia. His other medical conditions include asthma, seasonal allergies, and episodes of eczema. Current medications are budesonide-formoterol inhaler and loratadine as needed.

On physical examination, vital signs and other findings are normal.

Upper endoscopy is scheduled.

Which of the following is the most likely diagnosis?

(A) Barrett esophagus
(B) Eosinophilic esophagitis
(C) Esophageal cancer
(D) Peptic stricture
(E) Systemic sclerosis

Item 30

A 62-year-old man with compensated cirrhosis is evaluated at a follow-up visit. Six months ago, he was diagnosed with hepatitis C virus infection and treated with direct-acting antiviral agents. He experienced sustained viral response. Current liver ultrasound shows a small nodular liver compatible with cirrhosis and no masses.

On physical examination, vital signs and other findings are normal.

Which of the following is the most appropriate biannual surveillance modality?

(A) Abdominal MRI
(B) Contrast-enhanced CT
(C) Ultrasonography of liver
(D) No surveillance

Item 31

H

A 57-year-old woman is evaluated in the emergency department for a 9-month history of increasing abdominal pain that has worsened in the past week. After a total knee replacement 9 months ago, postoperative pain was managed with oxycodone. During this time she developed bilateral lower abdominal pain and constipation. Her constipation has improved with polyethylene glycol, but the abdominal pain continued to increase and is now diffuse and near-constant. Three days ago, she increased the frequency of oxycodone from three times daily to four times daily, and the abdominal pain intensified in frequency and severity. Despite this current level of pain, the patient is adamant that the only thing that helps her pain is oxycodone.

On physical examination, vital signs are normal. Diffuse abdominal tenderness without guarding is noted. Bowel sounds are hypoactive.

Findings on colonoscopy 6 months ago were normal. A CT scan obtained in the emergency department with oral and intravenous contrast shows moderate stool throughout the colon but no other abnormalities.

Which of the following is the most appropriate management?

(A) Add lubiprostone
(B) Add methadone
(C) Colonoscopy with biopsy
(D) Opioid discontinuation

Item 32

A 55-year-old man is evaluated at a follow-up visit. Two months ago he was admitted to the ICU for severe acute pancreatitis from alcohol use. CT during hospitalization revealed an edematous pancreas with fat stranding and peripancreatic fluid collections. He was discharged after 12 days. Two weeks before follow-up he had abdominal pain, and contrast-enhanced pancreas-protocol CT was performed. The scan demonstrated several hypodense lesions throughout the pancreas, including a 12-cm hypodense structure with a well-defined wall and no solid debris. The pancreatic duct was normal and no mass was identified. Today the patient reports feeling well; he has abstained from alcohol since hospitalization.

On physical examination today, vital signs and other findings are normal.

Which of the following is the most appropriate management?

(A) Endoscopic cystogastrostomy and necrosectomy
(B) Endoscopic retrograde pancreatography
(C) Endoscopic ultrasonography with fine-needle aspiration
(D) Surgical drainage
(E) Observation

Item 33

A 69-year-old man is evaluated in the ICU for the sudden onset of severe, constant periumbilical pain. He was admitted 2 days ago for new-onset atrial fibrillation with rapid ventricular rate and heart failure. He reports an urge to defecate but has not had a bowel movement in 2 days. Current medications are metoprolol, furosemide, losartan, and heparin.

On physical examination, blood pressure is 110/60 mm Hg, pulse rate is 112/min and irregular, and respiration rate is 24/min. The patient appears to have significant pain. Cardiac examination discloses an irregularly irregular rhythm. The abdomen is nondistended and soft, with mild tenderness to deep palpation in the mid abdomen; bowel sounds are present. Rectal examination reveals brown stool.

Laboratory studies:

Hemoglobin	13 g/dL (130 g/L)
Leukocyte count	13,000/μL (13.0×10^9/L), with 70% polymorphonuclear cells
Bicarbonate	17 mEq/L (17 mmol/L)
Lactate	2.1 mEq/L (2.1 mmol/L)

An abdominopelvic CT scan obtained without intravenous contrast is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Colonoscopy with biopsy
(B) CT angiography
(C) Doppler ultrasonography
(D) Magnetic resonance angiography

Item 34

A 60-year-old man is evaluated for a 4-month history of four to five loose bowel movements daily with antecedent abdominal cramps. He does not have nocturnal diarrhea, and the diarrhea has no relationship to eating. He also has a 1-year history of type 2 diabetes mellitus, treated with lifestyle interventions until 4 months ago, and hypothyroidism, diagnosed 10 years ago. He completed a course of amoxicillin for pneumonia 6 months ago. Current medications are metformin and levothyroxine.

On physical examination, vital signs are normal and other findings are unremarkable. His abdomen is soft, nontender, and nondistended; active bowel sounds are normal.

Erythrocyte sedimentation rate is 15 mm/h, leukocyte count is 4900/μL (4.9×10^9/L), and hematocrit is 44%.

Which of the following is the most likely cause of the patient's diarrhea?

(A) *Clostridioides difficile* colitis
(B) Crohn disease
(C) Metformin
(D) Microscopic colitis

Item 35

A 60-year-old man is evaluated at follow-up for elevated aminotransferase levels noted on laboratory testing for asymptomatic hepatomegaly. He has type 2 diabetes mellitus, hypertension, and hyperlipidemia. Current medications are metformin, hydrochlorothiazide, losartan, and atorvastatin. He consumes one to two alcoholic beverages weekly.

On physical examination, blood pressure is 143/80 mm Hg; other vital signs are normal. BMI is 37. Abdominal examination reveals hepatomegaly, no tenderness to palpation, and no splenomegaly.

Alkaline phosphatase level is 180 U/L, alanine aminotransferase level is 64 U/L, and aspartate aminotransferase level is 42 U/L. Complete blood count, serum albumin, and serum total bilirubin are normal.

Ultrasound shows a normal gallbladder without stones; normal-size bile ducts; and an enlarged, echogenic liver.

Which of the following is the most appropriate next step in management?

(A) Alcohol cessation
(B) Discontinuation of atorvastatin
(C) Initiation of pioglitazone
(D) Weight loss

Item 36

A 23-year-old woman is evaluated in the emergency department for a 3-day history of abdominal discomfort, nausea and vomiting, and pruritus. She is pregnant at 36 weeks' gestation.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 160/110 mm Hg, pulse rate is 98/min, and respiration rate is 22/min. Scleral icterus is noted. She has a gravid uterus.

Laboratory studies:

Hemoglobin	8.6 g/dL (860 g/L)
Platelet count	75,000/µL (75×10^9/L)
Alanine aminotransferase	130 U/L
Aspartate aminotransferase	110 U/L
Total bilirubin	3.4 mg/dL (58.1 µmol/L)
Direct bilirubin	1.6 mg/dL (27.4 µmol/L)
Lactate dehydrogenase	1600 U/L

Which of the following is the most appropriate management?

(A) Delivery of the fetus
(B) Plasma exchange
(C) Platelet transfusion
(D) Ursodeoxycholic acid therapy

Item 37

A 21-year-old man is evaluated for a 4-month history of diarrhea. Bowel movements are liquid and nonbloody and sometimes are preceded by lower abdominal cramps. He has near-daily bloating. Symptoms do not awaken him at night but improve with fasting. He reports no recent travel, antibiotic use, or weight loss.

On physical examination, vital signs are normal. Abdominal examination is normal.

Laboratory evaluation shows a hematocrit of 41% and negative fecal calprotectin level.

Which of the following is the most appropriate management?

(A) Colonoscopy
(B) Fructose breath test
(C) Stool culture
(D) Trial of lactose-free diet

H

Item 38

A 60-year-old woman is evaluated for follow-up of cirrhosis due to nonalcoholic steatohepatitis. Her cirrhosis has been complicated by ascites that has persisted despite escalating diuretic treatment. She has been adhering to a low-sodium diet. Current medications are furosemide and spironolactone.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 98/58 mm Hg, pulse rate is 68/min, and respiration rate is 16/min. She has scleral icterus and spider angiomas over her chest and upper back. Easily detectable ascites is present.

Serum creatinine level 2 weeks ago was 0.9 mg/dL (79.6 µmol/L). Current laboratory studies show a serum creatinine level of 1.9 mg/dL (167.9 µmol/L) and sodium level of 137 mEq/L (137 mmol/L).

Abdominal ultrasound shows a shrunken, irregular, and nodular liver; dilated portal vein; patent hepatic and portal vasculature; and ascites.

Assessment of urine output, urinalysis, and urine sodium concentration and results of a paracentesis are pending.

Which of the following is the most appropriate initial management?

(A) Discontinue diuretics
(B) Initiate fluid restriction
(C) Initiate propranolol
(D) Liberalize sodium intake

H

Item 39

A 59-year-old woman is evaluated in the emergency department for fever and jaundice. She has decompensated alcoholic cirrhosis with ascites. Current medications are furosemide and spironolactone.

On physical examination, temperature is 38.1 °C (100.7 °F), blood pressure is 100/60 mm Hg, and pulse rate is 60/min. Jaundice is present. Abdominal examination shows ascites and splenomegaly.

Laboratory evaluation shows a serum creatinine level of 1 mg/dL (88.4 µmol/L), blood urea nitrogen level of 30 mg/dL (10.7 µmol/L), and total bilirubin level of 4.1 mg/dL (70.1 mmol/L).

Diagnostic paracentesis for evaluation of ascitic fluid shows neutrophil count of 350/µL (0.35×10^9/L).

Which of the following is the most appropriate initial treatment?

(A) Fluoroquinolone
(B) Intravenous albumin
(C) Intravenous albumin and cefotaxime
(D) Trimethoprim-sulfamethoxazole

Item 40

A 44-year-old woman is evaluated for a 6-month history of nonbloody liquid stools five or six times daily. She reports a good appetite and no weight loss. She underwent cholecystectomy for acute cholecystitis 5 years ago.

On physical examination, vital signs are normal. Her abdomen is soft, nontender, and nondistended, with hyperactive bowel sounds.

Laboratory studies reveal a stool sodium level of 85 mEq/L (85 mmol/L) and stool potassium level of 4.5 mEq/L (4.5 mmol/L). Complete blood count and thyroid-stimulating hormone level are normal.

Which of the following conditions is most consistent with this patient's stool studies?

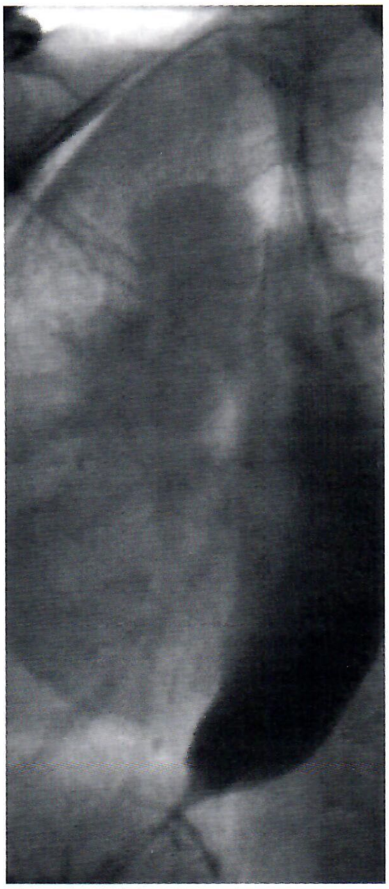
(A) Bile salt–induced diarrhea
(B) Enterotoxigenic *Escherichia coli* infection
(C) Fructose malabsorption
(D) VIPoma

Item 41

A 50-year-old woman is evaluated for worsening reflux. During the past 18 months she has experienced regurgitation after every meal. She has dysphagia with solid food and liquids. She has lost 2.3 kg (5.0 lb). Her symptoms have not responded to proton pump inhibitor therapy.

Vital signs and other physical examination findings are normal.

Esophagography demonstrates poor motility, with loss of the primary peristaltic wave and tapering at the distal esophagus associated with delayed clearance of the esophagus. Her esophagram is shown.



Which of the following is the most likely diagnosis?

- (A) Achalasia
- (B) Barrett esophagus
- (C) Eosinophilic esophagitis
- (D) Refractory gastroesophageal reflux disease
- (E) Viral esophagitis

Item 42

A 40-year-old woman is evaluated for a 3-month history of epigastric pain, bloating, abdominal fullness, nausea, and diarrhea 30 to 60 minutes after meals that is worse with larger meals. She sometimes experiences headaches and feels sweaty after larger meals. Symptoms usually improve gradually 30 minutes to 2 hours after eating. She has obesity, type 2 diabetes mellitus, and hypertension. She underwent sleeve gastrectomy 4 months ago. Current medications are omeprazole, promethazine, metformin, and lisinopril.

Vital signs and other physical examination findings are unremarkable. BMI is 35.

Upper endoscopy findings are notable only for gastric sleeve anatomy. Gastric biopsy specimens are negative for *Helicobacter pylori*. Duodenal biopsy specimens (for celiac disease) are normal. Result of a gastric emptying study is normal.

Which of the following is the most appropriate treatment?

- (A) Acarbose
- (B) Metoclopramide
- (C) Rifaximin
- (D) Smaller, more frequent meals

Item 43

A 55-year-old man is evaluated at a follow-up appointment. He had been experiencing intermittent epigastric abdominal pain for 3 months, and gallbladder ultrasound incidentally revealed a 4-cm lesion in his left liver. The gallbladder was normal, and his abdominal pain has spontaneously abated.

On physical examination, vital signs and other findings are unremarkable.

MRI with gadoxetate sodium contrast reveals a 4-cm mass consistent with a hepatic adenoma.

Which of the following is the most appropriate management?

- (A) Liver biopsy
- (B) Serial abdominal imaging
- (C) Surgical resection
- (D) Clinical observation

Item 44

H

A 40-year-old man is evaluated following discharge 6 weeks after hospitalization for an episode of upper gastrointestinal bleeding. During hospitalization, a proton pump inhibitor was initiated and subsequent upper endoscopy showed a healing Mallory-Weiss tear. He is currently asymptomatic. His only medication is omeprazole.

Physical examination findings are normal.

Which of the following is the most appropriate management?

- (A) Barium esophagography
- (B) Discontinuation of omeprazole
- (C) *Helicobacter pylori* testing
- (D) Upper endoscopy

Item 45

A 57-year-old man is evaluated for recurrent diarrhea and abdominal pain over the past 2 months. He was diagnosed with celiac disease 10 years ago when he presented with similar symptoms; at that time, symptoms resolved within

1 month of starting a gluten-free diet, which he has maintained since then. He has unintentionally lost 2 kg (5 lb) in the past 2 months.

On physical examination, vital signs and other findings are normal.

Laboratory testing reveals a tissue transglutaminase IgA level more than 30 times the upper limit of normal.

Assessment for which of the following conditions is the most appropriate initial management?

(A) Inadvertent gluten exposure
(B) Microscopic colitis
(C) Pancreatic insufficiency
(D) Small-bowel lymphoma

Item 46

A 55-year-old man is evaluated for a 2-week history of intermittent bright red blood per rectum and pain with defecation. He has marked anorectal discomfort with wiping, and blood is visualized in the toilet water and on toilet paper. His stools are firm and brown with bloody streaks. He also has chronic constipation treated with over-the-counter psyllium fiber supplement.

Inspection of the perineum reveals no thrombosed external hemorrhoid; however, while gently spreading the buttocks for inspection of the perianal region, the patient experiences exquisite pain.

Findings on screening colonoscopy 2 years ago were normal.

Which of the following is the most likely diagnosis?

(A) Anal fissure
(B) Angiodysplasia
(C) Internal hemorrhoids
(D) Rectal cancer

Item 47

A 29-year-old woman is evaluated at routine follow-up for chronic hepatitis B virus infection. She is asymptomatic, has no other medical conditions, and does not take any medications. She is negative for hepatitis C virus and HIV infections.

On physical examination, vital signs and other findings are normal.

Laboratory studies:

Alanine aminotransferase	89 U/L
Hepatitis B core antibody	Positive
Hepatitis B e antibody	Negative
Hepatitis B e antigen	Positive
Hepatitis B virus DNA	80,000 U/mL

Liver ultrasound is normal.

Which of the following is the most appropriate management?

(A) Antiviral therapy
(B) Clinical observation and surveillance
(C) Hepatitis B virus immune globulin
(D) Liver biopsy

Item 48

A 26-year-old woman is evaluated for a 4-week history of intermittent bright red blood per rectum and the feeling of incomplete evacuation. She has loose and blood-streaked bowel movements four or five times daily. She reports no other symptoms.

Vital signs and the remainder of the physical examination are normal.

Laboratory studies reveal a hemoglobin level of 11 g/dL (110 g/L) and a normal leukocyte count.

Colonoscopy reveals diffuse and symmetric inflammatory mucosal changes characterized by erythema and friability, with absent mucosal vascular pattern from the rectum to mid sigmoid. Biopsy specimens obtained from sigmoid and rectum show chronic colitis. Results of testing for *Clostridioides difficile* toxin are negative.

Which of the following is the most appropriate treatment?

(A) 5-Aminosalicylate (5-ASA) enemas
(B) 5-ASA suppositories
(C) Glucocorticoid enemas
(D) Oral 5-ASAs

Item 49

A 63-year-old woman is evaluated for heartburn, frequent nocturnal regurgitation, and solid food dysphagia of 5 years' duration. She has systemic sclerosis. Her only medication is omeprazole.

On physical examination, vital signs are normal. Dilated capillary vessels are noted on the face and palmar surface of the hands. Distal aspects of the fingers appear thick and inflamed.

Esophagram demonstrates poor motility with loss of the primary peristaltic wave, a patulous gastroesophageal junction, and gastroesophageal reflux to the level of the clavicles.

Endoscopy shows a mildly dilated esophagus with patulous lower esophageal sphincter. Stomach and duodenum appear normal.

Which of the following is the most appropriate treatment?

(A) Diltiazem
(B) Lifestyle changes and proton pump inhibitor
(C) Metoclopramide
(D) Laparoscopic fundoplication

Item 50

A 57-year-old man is evaluated for dysphagia. During the past year, he has noticed that swallowed meat occasionally gets stuck in his throat. More recently, softer foods have also been slow to move down after swallowing. He has lost 4.5 kg (9.9 lb) in the past 6 months. He has a many-year history of gastroesophageal reflux disease. His only medication is omeprazole.

On physical examination, vital signs are normal. BMI is 30. Other physical examination findings are unremarkable.

Laboratory evaluation reveals a mean corpuscular volume of 70 fL.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Barium esophagography
(B) CT of the chest
(C) Endoscopy with biopsy
(D) Esophageal motility study

Item 51

A 56-year-old man is evaluated for right-upper-quadrant abdominal pain of several months' duration. He otherwise has been well. He does not drink alcohol, has not been exposed to other hepatotoxins, and takes no medications.

On physical examination, vital signs are normal. Abdominal examination reveals hepatosplenomegaly. The remainder of the physical examination is normal.

Laboratory studies:

Platelet count	109,000/µL (109 × 10^9/L)
Alkaline phosphatase	450 U/L
Alanine aminotransferase	105 U/L
Aspartate aminotransferase	103 U/L

Chest radiograph shows bilateral hilar lymphadenopathy. Result of an interferon-γ release assay is negative.

Abdominal ultrasound shows a slightly enlarged, mildly nodular liver, with normal bile ducts. Spleen is 14 cm in length. Liver biopsy reveals changes of non-necrotizing hepatic granulomas without hepatic fibrosis.

Culture results of liver biopsy specimens are negative for fungal, *Brucella*, and *Coxiella burnetii* infections.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of abdomen
(B) Hepatobiliary iminodiacetic acid scintigraphy
(C) Magnetic resonance cholangiopancreatography
(D) Upper endoscopy

Item 52

A 68-year-old man is evaluated during hospitalization for epigastric abdominal pain and a 1-week history of black, tarry stools. His only medication is ibuprofen for osteoarthritis.

On physical examination, blood pressure is 110/60 mm Hg and pulse rate is 105/min. Other vital signs are normal. Abdominal examination reveals epigastric tenderness without guarding. Anorectal examination shows no blood or stool in the rectal vault.

Laboratory studies show a hemoglobin level of 10 g/dL (100 g/L).

Volume repletion with intravenous 0.9% saline is begun, along with intravenous administration of a proton pump inhibitor.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Capsule endoscopy
(B) Colonoscopy
(C) CT angiography
(D) Upper endoscopy

Item 53

A 70-year-old man is evaluated for follow-up 8 weeks after hospitalization for a bleeding duodenal ulcer. Upper endoscopy revealed multiple duodenal ulcers. Results of tests for *Helicobacter pylori* (gastric biopsy and serology) were negative. He currently has no abdominal pain or melena. He has osteoarthritis, with pain in the neck, hips, knees, and feet, which he had been treating with ibuprofen. The ibuprofen was discontinued during hospitalization and replaced with acetaminophen. His only other medication is omeprazole. He would like to resume an NSAID because acetaminophen is ineffective.

Which of the following is the most effective ulcer preventive strategy for this patient?

(A) Celecoxib and famotidine
(B) Celecoxib and omeprazole
(C) Naproxen and misoprostol
(D) Switch from ibuprofen to naproxen

Item 54

A 64-year-old man is evaluated in the emergency department for ascites. He has diabetes mellitus and cirrhosis associated with hemochromatosis, as well as a history of hepatic encephalopathy. Current medications are metformin, canagliflozin, lactulose, and rifaximin.

On physical examination, blood pressure is 106/76 mm Hg and pulse rate is 60/min; other vital signs are normal. The patient is alert. Jaundice, spider telangiectasia, and palmar erythema are present. Jugular venous distension and peripheral edema are present. Cardiac sounds are indistinct and lung sounds are diminished. Ascites is present.

Abdominal ultrasound shows a cirrhotic liver, splenomegaly, and abdominal ascites.

Paracentesis with analysis of ascitic fluid shows a leukocyte count of 100/µL (100 × 10^9/L), albumin level of 2.2 g/dL (22 g/L), and total protein level of 2.6 g/dL (26 g/L). Serum albumin level is 3.5 g/dL (35 g/L).

Which of the following is the most appropriate management?

(A) Ascitic fluid cytology
(B) Ascitic fluid triglyceride measurement
(C) Echocardiography
(D) Liver biopsy

Item 55

A 72-year-old woman is hospitalized for subacute onset of jaundice that developed 5 days ago on the second day of a cruise to Central America. She has no known liver disease and reports consuming fewer than three drinks per week. She has no abdominal pain, nausea, or vomiting. Five weeks

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ago she was treated with amoxicillin-clavulanate for an episode of acute diverticulitis.

On physical examination, vital signs are normal. Icterus and jaundice are observed. There are no signs of chronic liver disease. Mental status is normal, and no asterixis is seen.

Laboratory studies:

Alkaline phosphatase	200 U/L
Alanine aminotransferase	57 U/L
Aspartate aminotransferase	70 U/L
Total bilirubin	15 mg/dL (256.5 µmol/L)
INR	1.0

Right-upper-quadrant ultrasound shows no gallbladder stones or biliary dilation, a normal-size liver, and no masses.

Which of the following is the most likely diagnosis?

(A) Autoimmune hepatitis
(B) Drug-induced liver injury
(C) Hepatitis A virus infection
(D) Primary biliary cholangitis

Item 56

A 75-year-old man is evaluated for choking that started 3 months ago and has progressively worsened. He has trouble initiating the swallowing of pills and coughs when drinking liquids. He can eat soft foods without choking. He reports no heartburn, regurgitation, or chest pain. Parkinson disease was diagnosed 3 months ago. His only medication is carbidopa-levodopa.

On physical examination, vital signs are normal. A right, resting hand tremor, bradykinesia, rigidity, slow speech, and evidence of balance impairment are noted. The remainder of the examination is normal.

Which of the following is the most likely diagnosis?

(A) Achalasia
(B) Incarcerated paraesophageal hernia
(C) Oropharyngeal dysphagia
(D) Peptic stricture

Item 57

A 48-year-old man is evaluated for follow-up of cirrhosis due to hepatitis C virus (HCV) infection. He has ascites responsive to furosemide and spironolactone and recent-onset hepatic encephalopathy treated with lactulose. He has a MELD-Na (Model for End-Stage Liver Disease–sodium) score of 12. He takes no additional medications.

On physical examination, vital signs are normal. Physical examination reveals spider angiomas, abdominal distention, and a palpable liver edge below the right costal margin.

Laboratory studies:

Prothrombin time	14.6 s
Total bilirubin	2.6 mg/dL (44.5 µmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
HCV DNA	600,000 U/mL

Which of the following is the most appropriate management?

(A) Initiate protease inhibitor–based direct-acting antiviral therapy
(B) Initiate rifaximin therapy
(C) Limit dietary protein
(D) Refer for liver transplantation

Item 58

A 58-year-old woman is evaluated for treatment of hepatitis C virus (HCV) infection. She has unresectable metastatic pancreatic adenocarcinoma. She requests treatment of her HCV infection.

On physical examination, vital signs are normal. She has jaundice, icterus, and cachexia.

Which of the following is the most appropriate management?

(A) HCV antiviral treatment
(B) HCV viral load measurement and genotyping
(C) Testing for hepatitis B virus and HIV infections
(D) No further HCV-related testing or treatment

Item 59

A 39-year-old man is evaluated for diarrhea, characterized as passing five liquid stools daily for 3 months, accompanied by urgency and abdominal cramps. He reports no weight loss or rectal bleeding. He has a history of migraines. He has self-imposed a strict gluten-free diet for the past 5 years to prevent migraine. His only medication is daily ibuprofen to prevent migraine.

Vital signs and other findings on physical examination are normal.

Laboratory evaluation shows a hematocrit of 40% and normal fecal calprotectin level.

Which of the following is the most appropriate management?

(A) Colonoscopy
(B) Discontinuation of ibuprofen
(C) Tissue transglutaminase IgA measurement
(D) Video capsule endoscopy

Item 60

A 55-year-old man is evaluated at follow-up for iron deficiency anemia and positive result on stool guaiac testing. Despite excellent preparation and visualization, upper endoscopy and colonoscopy performed last week did not find the source of bleeding. He has no melena, hematochezia, or localizing symptoms. He has no other medical conditions and takes no medications.

Vital signs and other findings on physical examination are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT angiography
(B) Barium small-bowel follow-through
(C) Tagged red cell scintigraphy
(D) Video capsule endoscopy

Item 61

A 32-year-old man is evaluated for a relapse of ulcerative colitis unresponsive to increasing dosage of a 5-aminosalicylate. Symptoms remitted after 1 week of prednisone; after tapering the prednisone, however, symptoms returned.

On physical examination, vital signs are normal. Abdomen is nondistended, with left-lower-quadrant discomfort on deep palpation and no abdominal guarding.

Results of tests for tuberculosis, hepatitis B virus infection, and stool enteric pathogen panel are negative. Thiopurine methyltransferase enzyme activity is normal.

Colonoscopy shows changes consistent with ulcerative colitis from the rectum to the splenic flexure. Biopsy specimens show severe active chronic colitis without evidence of cytomegalovirus infection.

Which of the following is the most appropriate treatment?

(A) Azathioprine
(B) Azathioprine and infliximab
(C) Certolizumab
(D) Multimatrix budesonide

Item 62

A 55-year-old man is evaluated for follow-up after colonoscopy. He recently underwent colonoscopy for colon cancer screening, which revealed an 11-mm tubular adenoma. He has no family history of colorectal cancer. He has no symptoms and is taking no medications.

Which of the following is the most appropriate surveillance approach?

(A) Colonoscopy in 3 years
(B) Colonoscopy in 10 years
(C) Fecal DNA-based testing every 3 years
(D) Fecal occult blood testing annually

Item 63

A 54-year-old man is evaluated for an 8-week history of postprandial, gnawing, epigastric abdominal pain after every meal. Pain begins 30 minutes after eating, persists for 1 hour, and gradually resolves. He has had an associated 4.5-kg (9.9-lb) weight loss. He has hypertension, coronary artery disease, and peripheral vascular disease. Current medications are aspirin, atorvastatin, lisinopril, and metoprolol.

Vital signs are normal. BMI is 24. Physical examination reveals epigastric tenderness and an abdominal bruit.

Upper endoscopy findings are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Capsule endoscopy
(B) CT mesenteric angiography
(C) Gastric emptying study
(D) Ultrasonography of gallbladder

Item 64

A 75-year-old man is evaluated in the emergency department for several episodes of maroon blood per rectum and cramping abdominal pain of 18 hours' duration. He is admitted to the hospital and colonoscopy preparation is initiated. He has hypertension, atrial fibrillation, and coronary artery disease. At a colonoscopy performed 1 week ago, a 1-cm pedunculated polyp was removed from the transverse colon. Medications are apixaban, low-dose aspirin, metoprolol, and atorvastatin.

On initial physical examination, blood pressure was 95/40 mm Hg and pulse rate was 105/min and irregular. The abdomen was soft, with lower abdominal tenderness.

After admission and administration of 2 L of intravenous fluid, blood pressure is 110/60 mm Hg and pulse rate is 80/min.

Hemoglobin is 9 g/dL (90 g/L).

Which of the following is the most appropriate management of this patient's antiplatelet and anticoagulant therapy?

(A) Hold apixaban
(B) Hold apixaban and administer andexanet
(C) Hold aspirin and apixaban
(D) Hold aspirin and apixaban and administer andexanet

Item 65

An 80-year-old woman is evaluated in the emergency department. She has a 48-hour history of six maroon stools and mild lower abdominal pain. No bleeding is witnessed during 6 hours in the emergency department. She has hypertension and coronary artery disease. Current medications are atorvastatin, metoprolol, lisinopril, omeprazole, and low-dose aspirin.

On physical examination, blood pressure is 150/85 mm Hg and pulse rate is 70/min. Abdomen is soft and nontender.

Hemoglobin level is 10 g/dL (100 g/L).

Which of the following is the most appropriate diagnostic test?

(A) Colonoscopy
(B) CT angiography
(C) Tagged red cell scintigraphy
(D) Upper endoscopy

Item 66

A 25-year-old woman is hospitalized with a severe relapse of Crohn disease. Ileocolonic Crohn disease was diagnosed 2 years ago; it responded to dose-optimized azathioprine with prednisone. During the past year, three disease flares necessitated reintroduction of prednisone despite continuation of azathioprine. Her only medication is azathioprine.

On physical examination, vital signs are normal. Abdominal examination reveals right-lower-quadrant tenderness, with no mass. Anorectal examination is normal.

Abdominal CT scan shows only bowel wall thickening without significant luminal narrowing of the distal 8 cm of the terminal ileum and proximal colon. Colonoscopy shows severe mucosal inflammatory changes, with ulcerations in the terminal ileum and proximal colon.

Which of the following is the most appropriate treatment?

(A) Add budesonide
(B) Add infliximab
(C) Change azathioprine to 6-mercaptopurine
(D) Change azathioprine to sulfasalazine

Item 67

A 70-year-old man is evaluated for a 5-month history of bloating and nonbloody diarrhea. Diarrhea occurs three times daily. Bowel movements include oil droplets and require multiple flushes. He reports no abdominal pain. He has lost 2.3 kg (5 lb) since symptom onset.

On physical examination, vital signs are normal. Abdominal examination reveals diffuse tenderness to palpation without guarding.

On laboratory evaluation, hematocrit is 39%, tissue transglutaminase IgA level is normal, and the result of a *Giardia* enzyme immunoassay is negative.

Findings on colonoscopy with biopsy are normal. Abdominal CT obtained with oral and intravenous contrast shows multiple diverticula in the jejunum.

Which of the following is the most appropriate management?

(A) Eluxadoline
(B) Glucose breath test
(C) Stool testing for *Clostridioides difficile* toxin
(D) Upper endoscopy with duodenal biopsy

Item 68

A 49-year-old man is hospitalized for a 1-day history of melenic stools. He is taking ibuprofen daily to prevent migraine headaches.

On physical examination, vital signs and physical examination findings are normal.

Laboratory studies reveal a hemoglobin level of 11.2 g/dL (112 g/dL).

Upper endoscopy shows a 1.5-cm, clean-based, superficial duodenal ulcer. Findings from gastric biopsy specimens for assessment of *Helicobacter pylori* infection are pending.

Ibuprofen is stopped.

Which of the following is the most appropriate management?

(A) Intravenous proton pump inhibitor (PPI) and hospital observation for 72 hours
(B) Once-daily oral PPI, feeding, and hospital discharge
(C) Once-daily oral PPI, no feeding, and hospital observation for 72 hours
(D) Upper endoscopy repeated in 24 hours

Item 69

A 65-year-old woman is evaluated at a follow-up visit. She presented to the emergency department 2 weeks ago with a 2-day history of left-lower-quadrant abdominal pain. CT revealed diverticulitis and a 15-mm cystic structure in the body of the pancreas. She was discharged on oral antibiotics and now feels well. Colonoscopy is scheduled in 6 weeks. She has no other medical conditions and takes no medications. The radiology report indicates that the pancreatic cyst has all the imaging features of a serous cystadenoma.

Vital signs and other physical examination findings are normal.

Which of the following is the most appropriate management?

(A) Endoscopic ultrasonography and fine-needle aspiration
(B) MRI
(C) Surgical resection
(D) No further evaluation or intervention

Item 70

A 25-year-old woman is evaluated for a 6-month history of dyspepsia associated with early satiety, occasional epigastric burning, rare nausea, and postprandial bloating and belching. She has no melena or weight loss. She was born in the United States, has not recently traveled outside the country, and has no family history of gastrointestinal cancer.

On physical examination, vital signs are normal. Mild diffuse tenderness to palpation of abdomen is noted.

Complete blood count and results of liver function tests are normal.

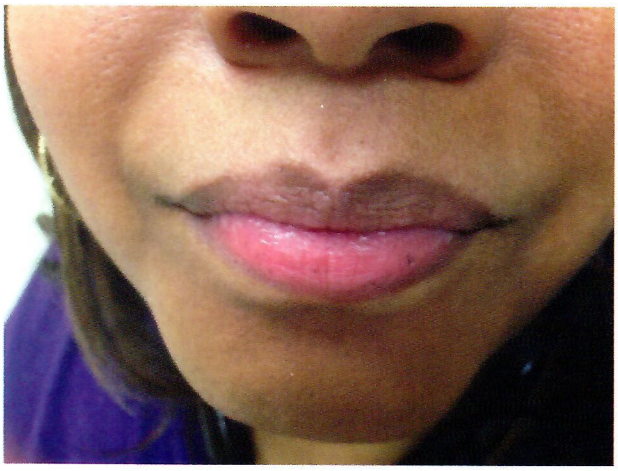
Which of the following is the most appropriate management?

(A) Abdominal CT
(B) Daily proton pump inhibitor
(C) *Helicobacter pylori* serology
(D) Stool antigen testing for *H. pylori*
(E) Upper endoscopy

Item 71

A 35-year-old woman is evaluated for follow-up of abdominal pain, which has prompted multiple emergency department visits. CT scans have revealed intussusception. Her mother was diagnosed with breast cancer at age 40 years. The rest of her family history is unknown.

On physical examination, vital signs are normal. Findings on lips are shown.



Which of the following is the most likely diagnosis?

(A) Adenomatous polyposis
(B) Hamartoma syndrome (Cowden syndrome)
(C) Juvenile polyposis syndrome
(D) Peutz-Jeghers syndrome

Item 72

A 55-year-old man is evaluated for follow-up of fundic gland polyps. Upper endoscopy was performed to screen for Barrett esophagus; it revealed a normal esophagus and approximately 10 to 15 polyps with a similar appearance in the gastric body (1-8 mm). Multiple biopsy specimens revealed fundic gland polyps without dysplasia. His only medication is omeprazole. Findings on colonoscopy are normal.

When should follow-up upper endoscopy be performed?

(A) 1 year
(B) 3 to 5 years
(C) 10 years
(D) No follow-up endoscopy

H

Item 73

A 60-year-old man is evaluated for follow-up of a gastric ulcer. He is asymptomatic. Upper endoscopy performed 4 weeks ago revealed a 1-cm, clean-based, cratered ulcer in the gastric antrum. Biopsy specimens from the ulcer margin were negative for malignancy. Random biopsy specimens from the stomach were negative for *Helicobacter pylori*. He has discontinued daily ibuprofen, previously used for osteoarthritis of the knees. Current medications are acetaminophen and omeprazole.

On physical examination, vital signs are normal. The abdomen is soft and nontender.

Which of the following is the most appropriate next step in management?

(A) Endoscopy after 8 weeks of proton pump inhibitor therapy
(B) Endoscopy after 12 weeks of proton pump inhibitor therapy
(C) Endoscopy in 6 to 12 months
(D) No follow-up endoscopy needed

Item 74

H

A 42-year-old woman is evaluated in the emergency department for right-upper-quadrant pain that has worsened over the preceding 2 days. She has otherwise been well and takes no medications.

On physical examination, temperature is 38.4 °C (101.2 °F). All other vital signs are normal. Abdominal examination reveals right-upper-quadrant tenderness and guarding.

Laboratory studies show normal hemoglobin level, elevated leukocyte count, and normal liver chemistries and lipase values.

An ultrasound demonstrates gallbladder wall thickening; a sonographic Murphy sign is present. There is no common bile duct dilation.

Piperacillin-tazobactam is initiated.

Which of the following is the most appropriate treatment?

(A) Cholecystectomy before hospital discharge
(B) Cholecystectomy in 4 weeks
(C) Emergent cholecystectomy
(D) Endoscopic retrograde cholangiopancreatography
(E) Percutaneous gallbladder drainage

Item 75

H

A 56-year-old man is evaluated in the emergency department for symptoms of progressive confusion for the past 2 days. He has a history of cirrhosis due to alcohol use but has been abstinent for the past 5 years. He also has a history of depression and anxiety. Escitalopram is listed as his only medication on the electronic medical record.

On physical examination, vital signs are normal. He is oriented to self but not time or place. Scleral icterus and asterixis are noted. The remainder of the examination is noncontributory.

Specimens are obtained for blood and urine cultures and a comprehensive metabolic profile.

Which of the following is the most appropriate next step in evaluation?

(A) CT of the head
(B) Electroencephalography
(C) Medication review and reconciliation
(D) Neuropsychiatric testing

Item 76

A 40-year-old woman is evaluated for intestinal metaplasia found on recent upper endoscopy to assess postprandial pain. No ulcers were visualized but generalized erythema and irregular mucosal pattern was noted. Biopsy specimens from the gastric antrum and gastric body showed extensive metaplasia, no dysplasia, and no *Helicobacter pylori*. Her father died of gastric cancer. Her only medication is omeprazole. She is of Korean descent.

Which of the following is the most appropriate next step in management?

(A) Discontinue omeprazole
(B) Initiate chemoprophylaxis with ascorbic acid
(C) Initiate chemoprophylaxis with aspirin
(D) Perform surveillance endoscopy

Item 77

A 64-year-old man is evaluated in the hospital 2 hours after diagnosis of a bleeding gastric ulcer and treatment with endoscopic clips. He also has atrial fibrillation, hypertension, and hyperlipidemia. Outpatient medications are warfarin, rosuvastatin, losartan, and hydrochlorothiazide. On hospitalization, intravenous omeprazole was initiated and warfarin was withheld.

On physical examination, vital signs are stable. Heart rhythm is irregularly irregular. The remainder of the examination is normal.

Laboratory studies reveal a hemoglobin level of 8 g/dL (80 g/L) and an INR of 2.2.

Which of the following is the most appropriate management?

(A) Begin intravenous heparin bridging therapy
(B) Discontinue warfarin permanently
(C) Reinitiate warfarin after 30 days
(D) Reinitiate warfarin within 7 days

Item 78

A 46-year-old woman is evaluated at a follow-up visit after being diagnosed with gallstones. She was evaluated in the emergency department 4 days ago for bothersome early satiation and postprandial fullness. A right-upper-quadrant ultrasound revealed several gallstones.

On physical examination, vital signs are normal. BMI is 37. Abdomen is nontender to palpation.

The ultrasound report describes multiple stones approximately 1 cm without gallbladder calcification, polyps, or biliary dilation.

Which of the following is the most appropriate management of the gallstones?

(A) Cholecystectomy
(B) Endoscopic retrograde cholangiopancreatography
(C) Magnetic resonance cholangiopancreatography
(D) Ursodeoxycholic acid
(E) Clinical observation

Item 79

A 40-year-old woman is evaluated at follow-up for stage I endometrial cancer diagnosed 6 weeks ago. Colon cancer was diagnosed in her mother at age 55 years and her maternal aunt at age 60 years.

The patient has had total abdominal hysterectomy and bilateral oophorectomy. Germline genetic testing confirmed a pathogenic mutation in *MSH2*.

Which of the following is the most appropriate screening strategy for this patient?

(A) Fecal DNA testing
(B) Fecal immunochemical test
(C) Upper endoscopy and colonoscopy
(D) Upper endoscopy, colonoscopy, and wireless capsule endoscopy

Item 80

A 60-year-old woman is evaluated for 6 months of progressive symptoms of dyspnea on exertion. She has cirrhosis due to nonalcoholic steatohepatitis complicated by ascites and esophageal varices. Current medications include propranolol, furosemide, and spironolactone.

On physical examination, vital signs are normal. Oxygen saturation is 99% with the patient breathing ambient air. On cardiac examination, central venous pressure is elevated. The pulmonic component of S_2 is increased in intensity. The lungs are clear to auscultation. The liver is enlarged and tender, and ascites is present.

Posteroanterior and lateral radiographs of the chest are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of chest
(B) Echocardiography
(C) Echocardiography with agitated saline
(D) Ventilation-perfusion scanning

Item 81

A 35-year-old woman is evaluated for nocturnal heartburn and regurgitation. She has a 5-year history of gastroesophageal reflux disease. She takes omeprazole every day 30 minutes before breakfast. She works as a musician and has concerts on weekends. After her concerts, she eats heavy meals at a late hour and experiences nocturnal symptoms that interfere with sleep. During the week, she has minimal symptoms when she maintains her normal routine. She has no other concerning symptoms. She does not smoke cigarettes.

On physical examination, BMI is 25.

Which of the following is the most appropriate additional management?

(A) Increase omeprazole to twice daily
(B) Laparoscopic fundoplication
(C) Lifestyle modifications
(D) Upper endoscopy
(E) Wireless pH testing

Item 82

A 66-year-old man is evaluated for relief of chronic back pain from a lumbar vertebral compression fracture documented on a recent radiograph. He has a history of cirrhosis, osteoporosis, and stage 2 chronic kidney disease. His only medication is a bisphosphonate.

On physical examination, vital signs are normal. The patient appears in mild distress because of back pain, with point tenderness over the fourth lumbar vertebra.

Laboratory studies show a serum total bilirubin level of 1.5 mg/dL (25.6 µmol/L) and serum creatinine level of 1.3 mg/dL (114.9 µmol/L).

Which of the following is the most appropriate treatment?

(A) Duloxetine
(B) Ibuprofen
(C) Low-dose opioid
(D) Physical therapy

Item 83

A 37-year-old man is evaluated in the emergency department for right-upper-quadrant pain, fever, and malaise of 3 days' duration. Until now he had been well.

On physical examination, his temperature is 38.9 °C (102.0 °F), blood pressure is 100/40 mm Hg, and pulse rate is 94/min. Jaundice is present. Abdominal examination reveals right-upper-quadrant tenderness and guarding.

Laboratory evaluation shows a normal hemoglobin value, an elevated leukocyte count, a total serum bilirubin level of 9 mg/dL (153.9 µmol/L), and normal lipase level.

Right-upper-quadrant ultrasound demonstrates a gallbladder with stones and no gallbladder wall thickening or pericolic fluid; common bile duct is somewhat dilated. A stone is visualized in the distal common bile duct.

Antibiotic therapy with piperacillin-tazobactam is initiated.

Which of the following is the most appropriate next step in management?

(A) Laparoscopic biliary drainage
(B) Magnetic resonance cholangiopancreatography
(C) Urgent cholecystectomy
(D) Urgent endoscopic retrograde cholangiopancreatography

Item 84

A 67-year-old man is evaluated for a 1-year history of vague, periodic epigastric pain. He reports no other symptoms. A trial of proton pump inhibitor therapy has not relieved symptoms.

Vital signs and other physical examination findings are unremarkable.

An abdominal ultrasound reveals a 1.5-cm polyp in the gallbladder, with no gallbladder wall thickening, fluid, stones, or sludge. No common bile duct dilation is seen.

Findings on upper endoscopy with gastric biopsy are normal.

Which of the following is the most appropriate management?

(A) Cholecystectomy
(B) Endoscopic retrograde cholangiopancreatography
(C) Hepatobiliary iminodiacetic acid scanning
(D) Ultrasonography in 6 months

Item 85

A 30-year-old man is evaluated for epigastric pain that is more severe with eating and has progressively worsened over the past 6 months. He has diminished oral intake, as well as occasional nausea and diarrhea. Family history includes stomach cancer in his father. A *Helicobacter pylori* test is negative, and proton pump inhibitor therapy with omeprazole has been ineffective. His only other medication is loperamide.

On physical examination, vital signs are normal. BMI is 24. The abdomen is tender to palpation. No guarding is noted.

Upper endoscopy findings are normal, as are biopsy specimens obtained from the stomach (for *H. pylori*) and duodenum (for celiac disease). Omeprazole is discontinued.

Which of the following is the most appropriate next step in treatment?

(A) Citalopram
(B) Famotidine
(C) Metoclopramide
(D) Nortriptyline

Item 86

A 56-year-old man is evaluated for a 2-day history of mild watery diarrhea occurring two or three times daily. He has not lost weight. Two days before symptoms developed, he returned from a 2-week trip to Southeast Asia.

On physical examination, temperature is 37.4 °C (99.4 °F), blood pressure is 120/80 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. Abdomen is soft, nontender, and nondistended. Bowel sounds are normal.

Information regarding oral rehydration therapy is provided.

Which of the following is the most appropriate additional management?

(A) Levofloxacin
(B) Loperamide
(C) Stool culture
(D) Stool molecular testing

Item 87

A 45-year-old man is evaluated after a positive result on fecal antigen testing for *Helicobacter pylori*, obtained 2 months after he completed eradication therapy for *H. pylori* gastritis, and duodenal ulcer documented by upper endoscopy. The patient was adherent to the initial eradication therapy, consisting of clarithromycin, amoxicillin, and omeprazole for 10 days. He is asymptomatic.

Which of the following is the most appropriate next step in management?

(A) Bismuth, tetracycline, metronidazole, and omeprazole for 14 days
(B) Clarithromycin, amoxicillin, and omeprazole for 14 days
(C) Clarithromycin, metronidazole, amoxicillin, and omeprazole for 14 days
(D) Repeat fecal antigen test in 4 weeks
(E) Repeat upper endoscopy and biopsy

H

Item 88

A 58-year-old man is hospitalized after having three black, loose stools in 1 day. He has no other medical conditions, takes no medications, and does not drink alcohol.

On physical examination, vital signs are normal. The patient appears comfortable, with a normal abdominal examination. Anorectal examination shows a small amount of black tarry stool in the rectal vault. The remainder of the examination is normal.

Upper endoscopy reveals a 1.5-cm gastric ulcer with a nonbleeding visible vessel, which is treated with endoscopic clips. Biopsy of the ulcer is performed, and results of testing for *Helicobacter pylori* infection are pending.

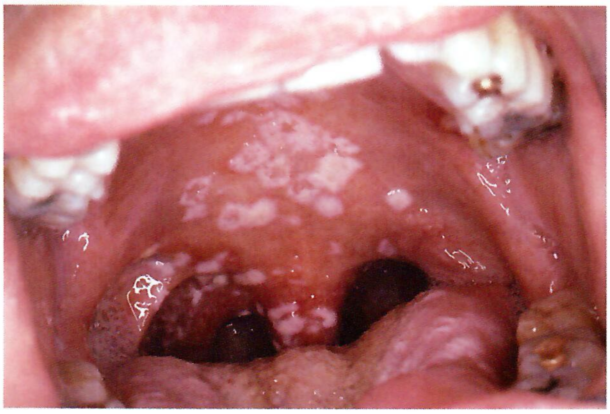
Which of the following is the most appropriate immediate treatment?

(A) Broad-spectrum antibiotics
(B) Esomeprazole, intravenously twice daily
(C) Octreotide, intravenously by continuous infusion
(D) Omeprazole, orally once daily

Item 89

A 43-year-old man is evaluated for difficulty with swallowing and painful swallowing. The pain began approximately 5 days ago and occurs with both solids and liquids. He has recently diagnosed HIV infection and is receiving antiretroviral therapy.

On physical examination, vital signs are normal. Oropharynx findings are shown.



The remainder of the examination is normal.

Previous laboratory studies revealed a CD4 cell count of 128/µL.

Which of the following is the most appropriate treatment?

(A) Ganciclovir
(B) Intravenous caspofungin
(C) Oral fluconazole
(D) Oral fluconazole and oral acyclovir
(E) Upper endoscopy with biopsy and cytologic brushings

Item 90

A 60-year-old woman is evaluated at follow-up for daily nausea, bloating and occasional vomiting after large meals, epigastric pain, and fullness. Upper endoscopy last week revealed some retained food in the stomach but no other significant findings, including *Helicobacter pylori* infection. She has a 10-year history of type 2 diabetes mellitus. Current medications are metformin and canagliflozin.

The hemoglobin A_{1c} level is 9%.

Which of the following is the most appropriate next step in management?

(A) Initiate erythromycin
(B) Initiate metoclopramide
(C) Obtain 4-hour gastric scintigraphy
(D) Obtain upper gastrointestinal barium series
(E) Repeat upper endoscopy once hemoglobin A_{1c} level is less than 7%

Item 91

A 56-year-old woman is evaluated for a 3-month history of watery, nonbloody diarrhea that occurs four times daily, usually after meals. Abdominal cramping precedes each bowel movement. She occasionally experiences rectal urgency. She has not lost weight. She also has osteoarthritis of the knees, self-treated with daily ibuprofen for the past 5 years.

On physical examination, vital signs and other findings are normal.

Colonoscopy reveals a normal-appearing colon. Biopsy specimens of normal-appearing ascending and sigmoid colon are notable for a marked increase in intraepithelial lymphocytes.

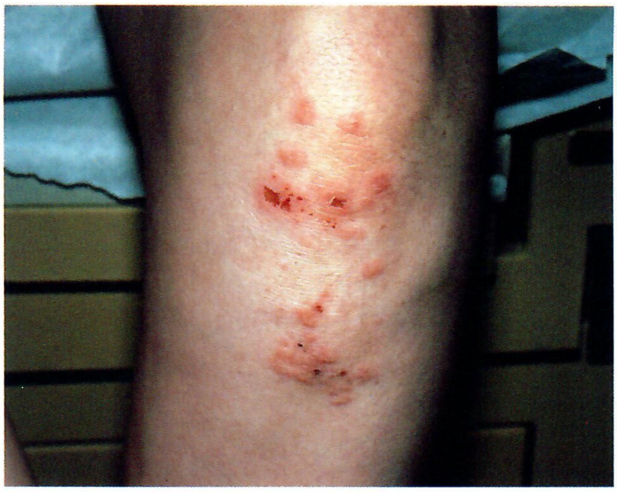
Which of the following is the most appropriate management?

(A) Check fecal calprotectin
(B) Discontinue ibuprofen
(C) Initiate oral budesonide
(D) Initiate oral prednisone

Item 92

A 27-year-old man is evaluated for a pruritic rash on his elbows and knees of 3 years' duration. Celiac disease was diagnosed 7 months ago. He started a gluten-free diet, and the diarrhea resolved but the rash has persisted. He is otherwise well and describes no additional symptoms. He is taking no medications.

On physical examination, vital signs are normal. Skin findings are shown.



Laboratory testing reveals a tissue transglutaminase IgA level of 2 U/mL (normal, 0-3 U/mL).

Skin biopsy findings are consistent with dermatitis herpetiformis.

Which of the following is the most appropriate management?

(A) Dapsone
(B) Hydrocortisone cream
(C) Hydroxychloroquine
(D) Measurement of glucose-6-phosphate dehydrogenase activity

Item 93

A 68-year-old man is evaluated in follow-up for constant, moderate epigastric pain that radiates to the back. Chronic pancreatitis was diagnosed 1 week ago. He is a 45-pack-year smoker. He does not currently drink alcohol.

On physical examination, vital signs are normal. Deep abdominal palpation elicits mild epigastric tenderness.

A pancreas-protocol CT scan demonstrated an atrophic pancreas with calcifications throughout, no masses, and no cystic lesions. The pancreatic duct caliber is normal.

NSAIDs and acetaminophen are recommended for pain.

Which of the following is the most appropriate additional treatment for pain?

(A) Oxycodone
(B) Pancreatic enzyme therapy
(C) Surgical pancreatic duct decompression
(D) Tobacco cessation

Item 94

A 65-year-old man is evaluated before hospital discharge. During hospitalization, he was treated for massive lower gastrointestinal bleeding. Fluid resuscitation relieved associated hypotension and tachycardia. The bleeding was attributed to diverticulosis, which was successfully treated during colonoscopy. He also has hypertension, type 2 diabetes mellitus, and hyperlipidemia. His medications include low-dose aspirin, hydrochlorothiazide, metformin, and rosuvastatin. Aspirin was held at the time of hospital admission. Family history includes stroke in his father.

Which of the following is the most appropriate management of this patient's aspirin therapy?

(A) Discontinue indefinitely
(B) Restart in 30 days
(C) Restart now
(D) Restart now and add omeprazole

Item 95

A 25-year-old woman is evaluated for frequent watery, nonbloody diarrhea that began 5 years ago. She has a 2-year history of arthralgia and headaches. Diarrhea, arthralgia, and headaches resolved after the patient started a gluten-free diet 1 year ago. Symptoms occasionally return if she accidentally consumes gluten.

Vital signs and other physical examination findings are normal.

Laboratory studies show a normal tissue transglutaminase IgA level. Results of testing for haplotypes *HLA-DQ2* and *HLA-DQ8* are positive for *HLA-DQ2*.

Which of the following is the most appropriate diagnostic test to perform next?

(A) *Clostridioides difficile* testing
(B) Repeat HLA testing after resumption of a gluten-containing diet
(C) Repeat tissue transglutaminase IgA measurement after resumption of gluten-containing diet
(D) Upper endoscopy and biopsy

Item 96

A 40-year-old woman was hospitalized 3 days ago with gallstone pancreatitis. Abdominal ultrasound at admission revealed multiple small gallstones in the gallbladder, a common bile duct that is normal in size (3 mm), and no choledocholithiasis. She was treated with intravenous fluids; her pain has resolved and she is now tolerating an oral diet.

On physical examination, vital signs and other findings are normal.

Current laboratory results are normal.

Which of the following is the most appropriate management?

(A) Endoscopic retrograde cholangiopancreatography
(B) Endoscopic ultrasonography
(C) Laparoscopic cholecystectomy before hospital discharge
(D) Laparoscopic cholecystectomy in 4 to 6 weeks
(E) Magnetic resonance cholangiopancreatography

Answers and Critiques

Item 1 Answer: C

Educational Objective: Treat autoimmune pancreatitis.

The most appropriate management is prednisone (**Option C**). The patient has painless jaundice with imaging features suggestive of type 1 autoimmune pancreatitis (AIP). CT findings that strongly suggest type 1 AIP include a diffusely enlarged pancreas with indistinct borders and delayed contrast enhancement. In comparison, imaging characteristics of pancreatic cancer include a low-density mass and dilatation and/or compression of the pancreatic duct associated with distal pancreatic atrophy. Endoscopic ultrasound with fine-needle aspiration, if pursued, shows greater than 10 IgG4-positive cells/hpf; this finding is consistent with a diagnosis of type 1 AIP, a manifestation of IgG4 disease. A significant elevation of serum IgG4 level is also helpful in diagnosing type 1 AIP. Most IgG4-related conditions are characterized by plasma cell infiltration of the tissues and subsequent clinical manifestations. AIP is a frequent manifestation of IgG4-related disease, but nearly any organ may be involved, including lymph nodes, salivary glands, and the biliary system. Retroperitoneal fibrosis may also be related to IgG4 disease. Initial treatment includes high-dose prednisone tapered over 2 to 3 months. Symptoms typically resolve within 2 to 4 weeks of therapy. Approximately 90% of patients achieve remission with oral glucocorticoids. Failure of clinical symptoms to respond to glucocorticoids suggests an incorrect diagnosis, and other causes should be investigated. Up to 60% of patients may relapse. Readministration of glucocorticoids or immunomodulators, such as 6-mercaptopurine, azathioprine, mycophenolate, or rituximab, may be used to treat recurrent AIP. Diagnostic criteria for AIP are known by the acronym HISORt (diagnostic Histology, suggestive Imaging, Serology with elevated serum IgG4, Other organ involvement, or Response to therapy with glucocorticoids). Type 2 AIP, or idiopathic duct-centric pancreatitis, does not demonstrate IgG4-positive cells but is instead characterized by granulocytic lesions. Type 2 AIP may be associated with inflammatory bowel disease.

The immunosuppressant azathioprine (**Option A**) may be used as a glucocorticoid-sparing agent to treat relapsing IgG4-related disease. Because of its slow onset, azathioprine is not used for induction therapy but is useful in the maintenance phase of therapy for recurrent disease.

Endoscopic retrograde cholangiopancreatography with biliary stent placement (**Option B**) is not required in AIP because jaundice should respond to glucocorticoids.

Although pancreatic adenocarcinoma and autoimmune pancreatitis may be mistaken for each other, in this patient the diagnosis appears certain on the basis of imaging characteristics and needle biopsy results. Total pancreatectomy (**Option D**) for pancreatic carcinoma is not indicated.

KEY POINTS

- CT findings that strongly suggest type 1 autoimmune pancreatitis include a diffusely enlarged pancreas with indistinct borders and delayed contrast enhancement.
- Initial treatment of type 1 autoimmune pancreatitis is high-dose oral prednisone tapered over 2 to 3 months.

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Item 2 Answer: A

Educational Objective: Diagnose primary biliary cholangitis.

The most appropriate diagnostic test to perform next is an antimitochondrial antibody (AMA) test (**Option A**). This patient most likely has primary biliary cholangitis (PBC), a diagnosis that is best established by positive results for AMA. PBC is an autoimmune disease affecting the small and medium bile ducts. It is often asymptomatic but can present with pruritus and fatigue. PBC is more common in women than men (female-to-male ratio is 9:1). Typically, the alkaline phosphatase level is elevated in PBC; if it is at least 1.5 times the upper limit of normal, a positive result on an AMA test establishes the diagnosis without the need for liver biopsy. Patients with PBC who are negative for AMA may test positive for other PBC-specific autoantibodies, including sp100 and gp210. Once PBC is diagnosed, first-line treatment is ursodeoxycholic acid, which results in histologic improvement, improves survival rates, and diminishes the need for liver transplantation.

Primary sclerosing cholangitis (PSC) is an autoimmune fibroinflammatory disease, primarily of large bile ducts. PSC is more common in men than in women and is associated with inflammatory bowel disease (IBD) in about 85% of cases. PSC should be suspected in patients with IBD who have elevated alkaline phosphatase levels. Some patients may also have elevated serum total bilirubin levels or total protein, reflecting the presence of hypergammaglobulinemia. PSC is associated with many autoantibodies, including anti–smooth muscle antibody (**Option B**). This otherwise well woman is more likely to have PBC than PSC, and measurement of anti–smooth muscle antibody is not indicated. Autoimmune hepatitis is a chronic inflammatory hepatitis that is more common in women than men and typically presents with abnormal aminotransferase enzyme levels. A positive antinuclear or anti–smooth muscle antibody result is more common in autoimmune hepatitis.

Liver biopsy (**Option C**) is not indicated because PBC is most often diagnosed noninvasively by serology. Only patients with strong suspicion for PBC and negative antibody results should undergo liver biopsy.

Autoimmune pancreatitis is a frequent manifestation of IgG4-related disease. Patients with autoimmune pancreatitis may present with abdominal pain or obstructive jaundice with or without a mass. Autoimmune pancreatitis may also be associated with secondary sclerosing cholangitis. This patient does not have abdominal pain or jaundice, and measuring serum IgG4 level (**Option D**) is not indicated.

KEY POINTS

- Primary biliary cirrhosis is most commonly diagnosed in women; it is often asymptomatic but can present with pruritus and fatigue.
- Diagnosis of primary biliary cholangitis is confirmed by elevation of the serum alkaline phosphatase level 1.5 times the upper limit of normal and the presence of antimitochondrial antibody.

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Item 3 Answer: B

Educational Objective: **Treat ascites in a patient with cirrhosis by stopping an ACE inhibitor.**

The most appropriate treatment is discontinuation of lisinopril (**Option B**). The development of ascites is often the first manifestation of decompensation of cirrhosis. Ascites results from portal hypertension and functional renal impairment, which leads to ineffective natriuresis and retention of sodium. In patients with ascites due to cirrhosis, the initial management of ascites consists of dietary sodium restriction, which may equalize the sodium balance in patients and prevent ascites. If this treatment does not resolve the sodium imbalance, a diuretic regimen with spironolactone and furosemide can be prescribed to increase natriuresis. Medications that decrease renal perfusion pressures, such as ACE inhibitors and angiotensin receptor blockers, can worsen ascites in patients with portal hypertension. Therefore, discontinuation of the ACE inhibitor lisinopril is the correct next step in the treatment of this patient. Other medications that should be used with caution or discontinued include β-blockers and NSAIDs. Propranolol has been shown to shorten survival in patients with refractory ascites. Prostaglandin inhibitors, such as NSAIDs, can reduce urinary sodium excretion in patients with cirrhosis and can induce azotemia.

Statins (**Option A**) for the treatment of dyslipidemia may increase hepatic aminotransferase levels. However, the overall benefits of these medications typically outweigh the potential harms, especially in patients with risk factors for coronary artery disease, such as in this patient with nonalcoholic steatohepatitis, type 2 diabetes, dyslipidemia, and hypertension. Therefore, discontinuation of atorvastatin is not appropriate.

Nonabsorbed disaccharides, such as lactulose (**Option C**), are initiated for the management of hepatic encephalopathy. This manifestation of cirrhosis can develop in the same population as patients with ascites. However, this cathartic is poorly tolerated and should not be initiated in a patient without symptoms referable to hepatic encephalopathy.

Patients with cirrhosis typically develop catabolic changes to their metabolism. The dietary protein needs of patients with decompensated cirrhosis exceed those of healthy persons, and dietary protein supplementation is indicated in this patient population. Therefore, a low-protein diet (**Option D**) should not be initiated for this patient.

KEY POINTS

- Medications that decrease renal perfusion pressures, such as ACE inhibitors, can worsen ascites in patients with portal hypertension.
- β-Blockers and NSAIDs should be used with caution or discontinued in patients with portal hypertension and ascites.

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Item 4 Answer: B

Educational Objective: **Categorize the phase of chronic hepatitis B virus infection.**

This patient is in the immune control phase of chronic hepatitis B virus (HBV) infection (**Option B**). Screening for chronic HBV infection is indicated in persons born or raised in regions with high rates of HBV infection, including Asia, Africa, the South Pacific, European Mediterranean countries, Eastern Europe, most of South America, Honduras, Guatemala, and the Middle East (except Israel and Cyprus). Screening will detect those who may benefit from treatment. Treatment is offered to selected patients in the immune active phase of infection. The four phases of infection are categorized on the basis of immune response to the virus: immune tolerant, immune active, immune control, and reactivation. The immune control phase of chronic HBV infection is also known as inactive chronic HBV infection. The immune control phase is characterized by normal serum alanine aminotransferase (ALT) measurement, indicating absence of liver inflammation; positive results for hepatitis B core (HBc) antigen IgG antibody, indicating previous infection; hepatitis B e antigen (HBeAg)–negative and anti-HBe–positive serology, indicating lack of viral replication and infectivity; and HBV DNA level less than 2000 U/mL, indicating immune control of viral replication and infection. This patient meets all the criteria for the immune control phase of chronic HBV infection. She does not require treatment.

The immune active phase of chronic HBV infection (**Option A**) is characterized by evidence of liver inflammation (elevated ALT level) and uncontrolled infection (HBV

DNA >2000 U/mL). HBeAg may be positive or negative in this phase. Depending on other factors, treatment may be indicated.

The immune tolerant phase (**Option C**) is acquired through vertical transmission. In this phase, HBeAg is positive, anti-HBeAg is negative, ALT level is normal, but HBV DNA level exceeds 1 million U/mL. Treatment is not recommended in this phase.

The reactivation phase (**Option D**) is characterized by loss of HBV immune control. It is recognized by a rising HBV DNA level compared with baseline or seroconversion of hepatitis B surface antigen (HBsAg) from negative to positive in patients who were previously HBsAg negative and anti-HBc positive. Reactivation may be the result of immunosuppression with immune modulators, cytotoxic chemotherapy, and drugs that deplete B lymphocytes, such as rituximab. Prophylactic treatment is typically recommended for select patients in the immune control phase who are at risk for reactivation.

KEY POINTS

- The four phases of chronic hepatitis B virus (HBV) infection are differentiated on the basis of immune response: immune tolerant, immune active, immune control, and reactivation.
- Patients in the immune control phase of chronic HBV infection, also known as inactive chronic HBV infection, generally do not require treatment.

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Item 5 Answer: A

Educational Objective: Treat hepatic abscess.

The most appropriate additional treatment is needle aspiration (**Option A**). Hepatic abscesses are typically found when patients present with fever, right-upper-quadrant abdominal pain, and malaise. Despite sometimes impressive findings on imaging, patients often have relatively mild and nontoxic symptoms. If an abscess is left untreated, septic shock can ultimately develop. Hepatic abscesses typically result from direct spread to the liver in the setting of biliary infection or portal venous spread of bacteria from abdominal infections, such as diverticulitis. Patients who are from areas of the world where amoeba are endemic, or patients who have traveled to these areas, should have serologic evaluation for *Entamoeba histolytica*. Serologic testing combined with abdominal imaging will confirm this diagnosis. In patients with pyogenic liver abscess, empiric broad-spectrum parenteral antibiotics that cover streptococci, enteric gram-negative bacilli, and anaerobes should be initiated before needle aspiration. Antibiotic therapy can be modified on the basis of culture results but is continued for several weeks. Abscesses 3 cm or greater in diameter typically do not resolve with antibiotic therapy alone, and aspiration of the abscess by percutaneous needle approach is warranted. In addition to aspiration, the patient should undergo evaluation to determine the cause of the abscess with abdominal imaging and diagnostic imaging of the biliary tree.

Hepatic abscesses that are less than 5 cm are not typically amenable to placement of a percutaneous drain (**Option B**).

Before the availability of interventional radiologic procedures, such as needle aspiration and drainage catheter placement, hepatic abscesses were often treated with surgical resection (**Option C**). This intervention is now rarely needed.

Continuation of antibiotics without drainage (**Option D**) is not appropriate because the size of the hepatic abscess (3.5 cm) requires drainage. Abscesses less than 3 cm in diameter typically resolve without additional intervention.

KEY POINTS

- In patients with pyogenic liver abscess, empiric broad-spectrum parenteral antibiotics that cover streptococci, enteric gram-negative bacilli, and anaerobes should be initiated.
- Hepatic abscesses 3 cm or greater in diameter typically do not resolve with antibiotic therapy alone, and aspiration of the abscess by percutaneous needle approach is warranted.

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Item 6 Answer: C

Educational Objective: Treat acute diverticulitis with hospitalization and intravenous antibiotics.

The most appropriate management for this patient with acute diverticulitis is hospitalization for intravenous antibiotics (**Option C**). Diverticulitis results from a diverticulum (herniation of the mucosa and submucosa through a weakness in the muscle wall) becoming blocked, trapping bacteria, and subsequently developing inflammation. This immunosuppressed patient has acute uncomplicated diverticulitis (no abscess, obstruction, or fistula). The medical management of diverticulitis is based on the degree of the patient's symptoms and severity of disease. Uncomplicated diverticulitis is treated with oral antibiotics (ciprofloxacin or metronidazole) and a liquid diet. Intravenous antibiotics with activities against gram-negative rods and anaerobic organisms are required in patients who cannot tolerate an oral diet; patients with severe comorbidities, advanced age, or immunosuppression; and patients for whom oral antibiotics have been ineffective. Typical regimens include ceftriaxone plus metronidazole, single-agent therapy with a β-lactam or β-lactam/β-lactamase

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inhibitor combination, or meropenem. This patient, who is immunosuppressed because of her prednisone and mycophenolate mofetil therapy, should be hospitalized for intravenous antibiotics.

Colonoscopy now (**Option A**) is contraindicated in acute diverticulitis. Guidelines recommend colonoscopy after the resolution of acute diverticulitis if a high-quality examination has not been performed recently; however, "recently" is not defined in the guidelines. Consideration of follow-up colonoscopy would be reasonable if more than 2 to 3 years have elapsed since the last examination.

Oral antibiotics (**Option B**) are considered adequate for stable, immunocompetent patients with uncomplicated diverticulitis. Clinical trials have failed to demonstrate superiority of intravenous antibiotics over oral antibiotics in this patient population. However, hospitalization and intravenous antibiotics are recommended for patients at higher risk for poor outcomes, such as patients with perforation, large abscesses, sepsis, or bowel obstruction or those who cannot tolerate liquid intake or have significant comorbid disease.

Surgery (**Option D**) is indicated for patients presenting with, or who develop, peritonitis or persistent sepsis. Surgery is not necessary in this patient with uncomplicated diverticulitis.

KEY POINTS

- Uncomplicated diverticulitis is treated with oral antibiotics (ciprofloxacin or metronidazole) and a liquid diet.
- Hospitalization and intravenous antibiotics are required to treat acute diverticulitis in patients who cannot tolerate an oral diet; patients with severe comorbidities, advanced age, or immunosuppression; and patients for whom oral antibiotics have been ineffective.

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Item 7 Answer: D

Educational Objective: **Treat alcoholic hepatitis.**

The most appropriate management is prednisolone (**Option D**). This patient has acute alcoholic hepatitis, a distinct clinical syndrome of severe steatohepatitis in the setting of chronic alcoholic liver disease. Acute alcoholic hepatitis often presents with fever, jaundice, tender hepatomegaly, and leukocytosis. The short-term mortality rate is high. In severe cases, as defined by a Maddrey discriminant function (MDF) score of 32 or greater or the presence of hepatic encephalopathy, treatment with prednisolone can be considered. The MDF score = 4.6 (prothrombin time [s] − control prothrombin time [s]) + serum total bilirubin (mg/dL). A meta-analysis of randomized studies showed that glucocorticoids were effective in reducing short-term mortality by 46%. This treatment should be considered in patients who do not have evidence of infection or gastrointestinal bleeding. This patient's MDF score is 35, and prednisolone should be considered. Prednisolone should be discontinued if there is no or only minimal response to therapy by day 7, as determined by the Lille model score (https://www.mdcalc.com/lille-model-alcoholic-hepatitis).

Although infections are common in patients with acute alcoholic hepatitis, in the absence of infection or suspicion of active infection, antibiotics (**Option A**) are not recommended.

Acute alcoholic hepatitis is most often diagnosed clinically, with liver biopsy (**Option B**) reserved for cases with diagnostic uncertainty. In this patient, the presence of fever, jaundice, tender hepatomegaly, and leukocytosis and a history of substantial alcohol consumption obviate the need for liver biopsy.

The 2018 American College of Gastroenterology guideline on alcoholic liver disease makes a conditional recommendation against the use of pentoxifylline (**Option C**) for patients with severe alcoholic hepatitis. Pentoxifylline should not be selected as initial therapy for this patient.

KEY POINTS

- Prednisolone is the treatment for severe alcoholic hepatitis, defined as a Maddrey discriminant function score of 32 or greater or the presence of hepatic encephalopathy.
- Patients with alcoholic hepatitis treated with prednisolone who do not respond after 7 days should have the prednisolone discontinued; otherwise, prednisolone should be continued for 28 days.

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Item 8 Answer: B

Educational Objective: **Identify the proper surveillance interval following removal of a serrated polyp.**

The most appropriate screening test to perform next is colonoscopy in 5 to 10 years (**Option B**). A surveillance interval of 5 to 10 years is appropriate for patients with one or two small (<10 mm) sessile serrated polyps without dysplasia. As the number or size of sessile serrated polyps increases, the surveillance interval decreases (3-5 years for 3-4 polyps or 3 years for 5-10 polyps, all <10 mm) and 3 years for polyps 10 mm or greater. This patient's colonoscopy revealed a single 7-mm sessile serrated polyp. It is critical that a polyp be completely removed during colonoscopy. Research suggests that up to 27% of interval colon cancers occur in the same colon section as the previous polypectomy, and another analysis that reexamined the colon of patients with sessile polyps greater than 2 cm demonstrated that 17.6% had residual neoplastic tissue, suggesting that incomplete polyp removal may be a cause for interval cancers. Quality of the baseline colonoscopy, which includes factors such as bowel preparation and adenoma detection rate by the endoscopist, may also affect risk for interval colon cancer.

The surveillance interval for multiple (≤20) small (<10 mm) hyperplastic polyps in the rectum or sigmoid colon or proximal to the sigmoid or rectum is 10 years, which is identical to the interval for colonoscopy in patient without polyps. Certain factors, however, may alter this recommendation. Serrated polyposis syndrome (SPS) is characterized by multiple serrated polyps throughout the colon. This syndrome has an uncertain genetic basis and can be diagnosed if a patient has either of the following during their lifetime: (1) five or more serrated polyps proximal to the rectum, all at least 5 mm in size, with two or more at least 10 mm in size, or (2) more than 20 serrated polyps throughout the colon, at least five located proximal to the rectum. Colonoscopy is recommended every year (**Option A**) in SPS, with removal of all polyps greater than 5 mm.

Interval stool-based testing with DNA testing (**Option C**) or fecal occult blood testing (**Option D**) is not recommended for patients with polyps identified and removed during colonoscopy.

KEY POINTS

- Colon cancer surveillance with colonoscopy every 5 to 10 years is appropriate for patients with one or two sessile serrated polyps less than 10 mm without dysplasia.
- As the number (>2) or size (≥10 mm) of sessile serrated polyps increases, the colon cancer surveillance interval decreases.

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Item 9 Answer: A

Educational Objective: **Diagnose celiac disease in a patient with IgA deficiency.**

The most appropriate management is measurement of serum anti–deamidated gliadin peptide IgG antibodies (**Option A**). This patient is at high risk for celiac disease, given her chronic diarrhea, low weight, osteoporosis, and family history. Tissue transglutaminase IgA antibody is the preferred serologic test for celiac disease in general, but its sensitivity is diminished in the setting of selective IgA deficiency. This patient's undetectable total IgA level indicates that she has selective IgA deficiency, so IgG serology should be used. Available IgG serologies are antibodies to deamidated gliadin peptide or tissue transglutaminase. If the anti–deamidated gliadin peptide IgG antibody level is elevated, upper endoscopy with duodenal biopsy should be performed; the presence of villus atrophy indicates a diagnosis of celiac disease, for which a gluten-free diet should be prescribed.

Testing for anti-gliadin antibodies (IgA and IgG) (**Option B**) should not be done because of its low sensitivity and specificity compared with testing for antibodies to deamidated gliadin peptide.

Before a gluten-free diet (**Option C**) is recommended, it is crucial to determine the celiac disease status of the patient because the sensitivity of serologies and duodenal biopsy declines after institution of a gluten-free diet. This patient's celiac disease status has not yet been clarified—she has selective IgA deficiency, and IgG serologies have not yet been performed.

Current guidelines recommend that *HLA-DQ2* and *HLA-DQ8* testing (**Option D**) should not be used routinely as part of the initial diagnosis of celiac disease; if this testing is done and results are positive, patients should still be serologically tested for celiac disease. Genetic testing is most valuable for patients who have not had serologic testing for celiac disease before starting a gluten-free diet and when the results of celiac-specific serology and histology are discrepant.

KEY POINT

- In patients with selective IgA deficiency undergoing testing for celiac disease, IgG antibodies to deamidated gliadin peptide or tissue transglutaminase should be used.

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Item 10 Answer: A

Educational Objective: **Diagnose Budd-Chiari syndrome.**

The most appropriate diagnostic test to perform next is abdominal Doppler ultrasonography (**Option A**). The development of Budd-Chiari syndrome is heralded by right-upper-quadrant abdominal discomfort, hepatomegaly, and ascites. Thrombosis of the hepatic veins leads to hepatic congestion and increased portal pressures, resulting in ascites. Risk factors for Budd-Chiari syndrome include hypercoagulable states, such as myeloproliferative neoplasms, pregnancy, and the use of oral contraceptives. Budd-Chiari syndrome can be diagnosed with Doppler ultrasonography of the abdomen, which demonstrates absence of flow in the hepatic veins as well as hepatic congestion. Typically, the caudate lobe of the liver will develop hypertrophy because the venous drainage of this segment of the liver is directly into the inferior vena cava rather than through the hepatic veins. Long-term anticoagulation is required in patients with Budd-Chiari syndrome, although bleeding risks are significant in patients with acute or chronic liver disease, portal hypertension, and esophageal varices. Angioplasty of the hepatic veins and/or placement of a transjugular intrahepatic portosystemic shunt (TIPS) can be used to reestablish adequate hepatic venous drainage. If liver failure develops, liver transplantation may be considered.

Abdominal radiography (**Option B**) can demonstrate bowel obstruction or intestinal ileus but would not be helpful in the diagnosis of hepatic vein thrombosis.

Hepatobiliary iminodiacetic acid scintigraphy (**Option C**) is used to evaluate for gallbladder obstruction or a bile leak after an intervention on the biliary tree. This patient's acute onset of tender hepatomegaly and ascites is not compatible with intermittent, colicky gallbladder pain, and hepatobiliary scintigraphy is not indicated.

Noncontrast abdominal CT (**Option D**) is not helpful when there is concern for vascular disease in the abdomen. Intravenous contrast is essential for evaluating the patency of the hepatic artery, portal veins, and hepatic veins. Contrast-enhanced abdominal CT can help elucidate the extent of vascular thrombosis and potential use of a TIPS for opening the hepatic veins to decompress the liver; without intravenous contrast, however, CT would not be appropriate in this setting. In most patients, Doppler ultrasonography is adequate for evaluation of Budd-Chiari syndrome and does not require contrast administration or radiation exposure.

KEY POINTS

- Budd-Chiari syndrome is suggested by right-upper-quadrant abdominal discomfort, hepatomegaly, and ascites.
- Budd-Chiari syndrome can be diagnosed with Doppler ultrasonography of the abdomen; it demonstrates absence of flow in the hepatic veins as well as hepatic congestion.

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Item 11 Answer: A

Educational Objective: Prevent transmission of hepatitis A virus.

The most appropriate preventive measure is administration of the hepatitis A virus (HAV) vaccine (**Option A**). HAV is transmitted by the fecal-oral route and causes a self-limited illness. Risk factors for transmission include international travel, contact with household members with HAV infection, men who have sex with men, homelessness, and exposure to day care or institutionalized settings. HAV incidence declined dramatically after introduction of universal childhood HAV vaccination, but rates have recently increased among unvaccinated people, especially those reporting homelessness or drug use. This unvaccinated patient has been exposed to a roommate with acute HAV infection and so is at risk for infection. Persons who have recently been exposed to HAV and have not been immunized should receive postexposure prophylaxis, consisting of the HAV vaccine, as soon as possible after exposure, preferably within 2 weeks. The HAV vaccine is recommended for prophylaxis in persons aged 12 months or older. For long-term immunity, the HAV vaccine series should be completed with a second dose at least 6 months after the first dose; however, the second dose is not necessary for postexposure prophylaxis.

According to the CDC, the HAV vaccine for postexposure prophylaxis provides numerous public health advantages compared with HAV immune globulin (**Option B**), including the induction of active immunity and longer duration of protection, ease of administration, and greater acceptability and availability.

For exposed patients older than 40 years, HAV vaccine and HAV immune globulin (**Option C**) may be coadministered, depending on individual risk assessment. Combined therapy (administered at different sites) is a consideration because of the limited vaccine efficacy in this age group and the greater severity of illness in older adults. HAV immune globulin may also be administered to persons at high risk for complications, including those with chronic liver disease and immunosuppression. Because this young patient does not have these risk factors, HAV immune globulin is not necessary.

Although HAV infection is usually a self-limited illness, patients may experience considerable morbidity; fulminant hepatic failure, although rare, can occur. Postexposure vaccination will effectively prevent infection in this patient and is recommended rather than providing no preventive measures (**Option D**).

KEY POINTS

- Nonimmune persons exposed to hepatitis A virus (HAV) should receive postexposure prophylaxis with HAV vaccine as soon as possible after exposure.
- Postexposure prophylaxis with both HAV vaccine and HAV immune globulin may be considered for nonimmune patients older than 40 years.

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Item 12 Answer: A

H

Educational Objective: Diagnose acute pancreatitis.

The most appropriate management is contrast-enhanced CT (**Option A**). This patient probably has acute pancreatitis, the diagnosis of which requires at least two of the following: (1) acute-onset abdominal pain characteristic of pancreatitis (severe, persistent for hours to days, and epigastric in location, often radiating to the back); (2) elevation in pancreatic enzymes (typically lipase) three times the upper limit of normal or higher; and (3) imaging findings characteristic of acute pancreatitis, including peripancreatic fat stranding and inflammation as well as peripancreatic edema. Serum

CONT.

amylase and lipase levels may be elevated in nonpancreatic conditions (e.g., kidney disease, acute appendicitis) and therefore are not specific for acute pancreatitis. This patient has typical symptoms, but his lipase levels do not meet the threshold for diagnosis. Therefore, cross-sectional imaging is recommended to confirm the diagnosis. Cross-sectional imaging is also helpful to assess patients for other conditions that might mimic acute pancreatitis and to evaluate patients with atypical symptoms. Preferred imaging modalities include contrast-enhanced CT and MRI.

Routine use of antibiotics (**Option B**) is not warranted in acute pancreatitis unless there is evidence of extrapancreatic infection, such as ascending cholangitis, bacteremia, urinary tract infection, or pneumonia. Prophylactic antibiotics do not affect the rates of important outcomes, such as organ failure and hospital length of stay.

Endoscopic ultrasonography (**Option C**), in which an ultrasound probe is placed in the stomach and small intestine to better visualize the pancreas and biliary system, is not typically used in the initial diagnosis of pancreatitis because of its invasive nature.

Once a diagnosis of pancreatitis is confirmed, patients should undergo an assessment for the cause of acute pancreatitis. Biliary disease and alcohol are the most common causes of acute pancreatitis. Transabdominal ultrasonography is the preferred imaging modality to assess for a biliary cause of acute pancreatitis. Triglyceride levels (**Option D**) should be measured in patients without a biliary cause of acute pancreatitis; a triglyceride level exceeding 1000 mg/dL (11.3 mmol/L) can be considered the cause of the acute pancreatitis. Because the diagnosis of acute pancreatitis has not been established and the biliary tree has not been evaluated, measurement of triglyceride levels is premature.

KEY POINTS

- The diagnosis of acute pancreatitis requires at least two of the following: (1) acute-onset abdominal pain characteristic of pancreatitis, (2) elevation in pancreatic enzymes at least three times the upper limit of normal, and (3) findings on cross-sectional imaging characteristic of acute pancreatitis.
- Routine use of antibiotics is not warranted in acute pancreatitis.

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Item 13 Answer: A

Educational Objective: Diagnose multiple endocrine neoplasia type 1.

This patient should undergo genetic testing for multiple endocrine neoplasia type 1 (MEN1) (**Option A**). Although most pancreatic neuroendocrine tumors (NETs) are sporadic, some are associated with hereditary endocrinopathies, such MEN1, von Hippel-Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis. Among these inherited endocrinopathies, MEN1 is most frequently associated with pancreatic NETs (≥80%), whereas pancreatic NETs occur in 1% to 20% of the other inherited endocrinopathies. MEN1 is a rare heritable disorder classically characterized by a predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells, including insulinoma, as seen in this patient. MEN1 is clinically diagnosed by the presence of two or more primary MEN1 tumor types. In patients who have family members with a diagnosis of MEN1, the presence of a single MEN1-associated tumor satisfies the diagnostic criteria for MEN1. Pancreatic NETs account for the greatest proportion of deaths in patients with MEN1, and gastrinoma is the most common of the functioning NETs. However, most gastrinomas are located in the duodenal wall, not the pancreas. Insulinomas are the second most common NET and the most common pancreatic NET; they tend to be small and may be multiple. Sporadic insulinomas occur in patients age 40 years and older; therefore, the diagnosis of insulinoma in a younger patient is cause to screen for MEN1.

A defect of the *RET* proto-oncogene is responsible for the clinical variations of MEN type 2 (MEN2) (**Option B**), which involve tumors of the thyroid, parathyroid, and adrenal glands. MEN2 is not associated with NETs of the pancreas, and genetic testing for the *MEN2* gene is not indicated.

Neurofibromas present as soft, skin-colored papules. Other cutaneous manifestations of neurofibromatosis type 1 (**Option C**) include café-au-lait macules and axillary freckling. Nearly all patients with tuberous sclerosis (**Option D**) have one or more of the characteristic skin lesions, including hypopigmented macules, angiofibromas, or a brown fibrous plaque on the forehead. Genetic testing for these disorders is not indicated in the absence of these cutaneous findings.

KEY POINT

- Sporadic insulinomas tend to occur in patients age 40 years and older; therefore, the diagnosis of insulinoma in a younger patient is cause to screen for multiple endocrine neoplasia type 1.

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Item 14 Answer: A

Educational Objective: Evaluate chronic constipation.

The most appropriate management is colonoscopy (**Option A**). Constipation is one of the most common gastrointestinal symptoms, affecting 20% of the general population. Constipation can present with symptoms including infrequent, difficult, or incomplete defecation, and it can be acute or chronic. The patient's history is compatible with chronic constipation. Constipation can be secondary or functional (idiopathic). Medications are the most common cause of secondary constipation. Other causes of this common condition include mechanical obstruction, systemic illnesses, altered physiologic states, and psychosocial conditions. Once secondary causes have been excluded, chronic constipation is considered functional. Functional constipation is subtyped into categories of slow transit, normal transit, or dyssynergic defecation. Slow-transit constipation is defined as the delayed passage of fecal contents through the colon based on objective transit testing. Normal-transit constipation is functional constipation in which colonic transit times are adequate. Dyssynergic defecation refers to difficulty with or inability to expel stool as a result of some combination of abnormalities in contraction and/or relaxation of the muscles of the pelvic floor during defecation. Colonoscopy is the initial evaluation of constipation in elderly patients with acute constipation and patients with unintentional weight loss, family history of colorectal cancer, unexplained anemia, and age older than 50 years with no previous colonoscopy. This patient is age 52 years, and colonoscopy should be performed as the initial study to evaluate for mechanical causes of constipation.

Treatment options for chronic constipation include serotonergic prokinetic agents (prucalopride [**Option B**]), bulking agents (psyllium [**Option C**]), stimulant laxatives (senna, bisacodyl), osmotic laxatives (polyethylene glycol, lactulose, sorbitol), stool softeners (docusate), secretagogues (lubiprostone, linaclotide, plecanatide), and/or biofeedback. These therapeutic modalities are appropriate after evaluation for a cause of constipation.

Physiologic testing, including colon transit testing with a radiopaque marker study (**Option D**), scintigraphy, or the wireless motility capsule, is reserved for patients with constipation symptoms that do not respond to initial trials of lifestyle modification and laxative therapy.

KEY POINTS

- Constipation can be secondary or functional (idiopathic); medications are the most common cause of secondary constipation.
- Colonoscopy is the initial evaluation of constipation in elderly patients with acute constipation and patients with unintentional weight loss, family history of colorectal cancer, unexplained anemia, and age older than 50 years with no previous colonoscopy.

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Item 15 Answer: A

Educational Objective: Evaluate for inflammatory bowel disease in a patient with primary sclerosing cholangitis.

The most appropriate management is colonoscopy (**Option A**). The clinical presentation of primary sclerosing cholangitis (PSC) varies. Many patients are asymptomatic, whereas others are diagnosed after an evaluation of abnormal laboratory test results demonstrating a cholestatic pattern of liver injury. Symptomatic patients present with fatigue and pruritus. Clinical findings vary as well. Asymptomatic patients may have no findings, and others may have jaundice, hepatomegaly, splenomegaly, and excoriations related to pruritus. PSC is associated with inflammatory bowel disease (IBD) in approximately 85% of cases. Therefore, all patients with PSC without known IBD should have colonoscopy with biopsies at the time of PSC diagnosis. Common colonoscopy findings in patients with PSC and IBD include mild pancolitis with rectal sparing and backwash ileitis. Because of the higher risk for colon cancer in these patients, surveillance colonoscopy with biopsies is also recommended every 1 to 2 years. Patients with PSC have a 15% lifetime risk for cholangiocarcinoma. Annual or biannual magnetic resonance cholangiopancreatography (MRCP) and measurement of the carbohydrate antigen 19-9 level are recommended for cholangiocarcinoma surveillance. The incidence of cholangiocarcinoma is highest in the first 2 years after PSC is diagnosed. There is also an increased risk for gallbladder cancer in PSC, and regular annual screening with ultrasonography is recommended.

PSC is most commonly diagnosed by MRCP. Endoscopic retrograde cholangiopancreatography (ERCP) (**Option B**) is indicated in patients who have associated jaundice, worsening pruritus, cholangitis, or a dominant stricture or bile duct mass on MRCP. This patient has no indication for ERCP at this time.

Liver biopsy (**Option C**) is useful in patients for whom PSC is suspected but the MRCP result is normal. In this situation, small-duct PSC not seen on MRCP may be diagnosed with liver biopsy. This patient has no indication for liver biopsy because MRCP established the diagnosis.

Liver transplantation (**Option D**) should be considered for patients with PSC and decompensated cirrhosis, recurrent bacterial cholangitis, and hilar cholangiocarcinoma. Transplant outcomes for patients with PSC are excellent, with 1-year survival rates of at least 90% and recurrence rates of approximately 20% at 5 years after liver transplantation. This patient does not have an indication for liver transplantation.

KEY POINTS

- Primary sclerosing cholangitis (PSC) is associated with inflammatory bowel disease (IBD) in approximately 85% of cases; therefore, all patients with PSC without known IBD should have colonoscopy with biopsies at the time of PSC diagnosis.
- Patients with PSC have a 15% lifetime risk for cholangiocarcinoma; annual or biannual magnetic resonance cholangiopancreatography and carbohydrate antigen 19-9 measurement is recommended for cholangiocarcinoma surveillance.

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Item 16 Answer: B

Educational Objective: Treat acute pancreatitis with initiation of oral feeding.

The most appropriate management is initiation of oral feeding (**Option B**). The patient has acute pancreatitis. The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute-onset abdominal pain characteristic of pancreatitis, (2) serum lipase or amylase levels elevated at least three times the upper limit of normal, and (3) characteristic imaging findings. She received intravenous resuscitation overnight, which typically consists of 250 to 500 mL/h of normal saline or lactated Ringer solution, with fluid boluses as needed for severe volume depletion. Treatment with intravenous fluids should be aimed at avoiding hypovolemia and maintaining adequate organ perfusion. Goal-directed therapy allows for titration of fluids to particular biochemical and clinical targets, including blood pressure, pulse rate, urine output, blood urea nitrogen, and hematocrit. This patient initially had risk factors for severe disease, including a hematocrit greater than 44%, which has improved with volume resuscitation. Overall, her pain is improving and oral feeding should therefore be considered. Patients with acute pancreatitis should resume feeding when pain improves and any nausea or vomiting subsides. Oral feeding is preferred, and guidelines recommend starting oral feeding within 24 hours.

If patients with acute pancreatitis do not tolerate oral feeding, enteral tube feeding (**Option A**) should be considered within 72 hours. Historically, this approach included placement of a nasojejunal tube to avoid stimulation of the pancreas. More recent data suggest that nasogastric tube placement and feedings are easier to administer than nasojejunal feeding and are as efficacious. In this patient, however, oral feeding should be attempted before enteral feeding is considered.

In the past, management of acute pancreatitis included keeping patients on nothing-by-mouth status (**Option C**) to prevent stimulation of the pancreas. However, more recent evidence has demonstrated a benefit to early feeding; this approach may promote a healthy mucosal barrier and avoid translocation of gut bacteria, which can result in local and systemic infection.

Transfusion of packed red blood cells (**Option D**) is not required at this time. Although complications of pancreatitis may include gastrointestinal bleeding (e.g., splenic vein thrombus leading to varices or pseudoaneurysm formation followed by rupture of an arterial wall), this patient is hemodynamically stable and does not exhibit signs or symptoms of acute gastrointestinal bleeding. She was intravascularly depleted at the time of hospitalization, and fluid resuscitation led to an expected decrease in hematocrit.

KEY POINTS

- Patients with acute pancreatitis should resume oral feedings when pain improves and any nausea or vomiting subsides.
- If patients with acute pancreatitis do not tolerate oral feeding, enteral feeding should be considered within 72 hours.

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Item 17 Answer: D

Educational Objective: Screen for Barrett esophagus.

The most appropriate management is upper endoscopy (**Option D**). This patient has longstanding (≥5 years) gastroesophageal reflux disease (GERD) along with multiple risk factors for esophageal cancer, including male sex, age older than 50 years, hiatal hernia, obesity with intraabdominal distribution of fat, and tobacco use. Endoscopy to assess for Barrett esophagus is indicated. The diagnosis of Barrett esophagus is confirmed by the finding of salmon-colored mucosa on endoscopy with columnar epithelium with acid-mucin–containing goblet cells on histopathology. Barrett esophagus progresses as follows: intestinal metaplasia, indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, intramucosal carcinoma, and, finally, invasive adenocarcinoma. Patients with high-grade dysplasia and confirmed low-grade dysplasia should undergo treatment to eradicate all neoplastic and at-risk epithelium. Patients with Barrett esophagus without dysplasia should undergo surveillance endoscopy every 3 to 5 years to monitor for dysplasia or precancerous changes.

Bariatric surgery (**Option A**) might be a reasonable option to treat this patient's obesity. However, before that decision is made, screening this higher-risk patient for esophageal cancer should be performed and cancer should be treated, if found.

In the setting of GERD, an esophageal motility study (**Option B**), such as esophageal manometry, would be indicated to rule out a motility disorder before antireflux surgery. This patient reports good symptom control with medical therapy, however, and does not require antireflux surgery. Furthermore, he has no other symptoms, such as dysphagia, that suggest a motility disorder. Therefore, a motility study is not indicated.

Surgery is not required because this patient's GERD is currently well controlled with medical therapy. Surgery is infrequently required for GERD; indications include failure of optimal proton pump inhibitor therapy, desire to stop medication, and intolerable medication side effects. Surgical treatments for GERD are laparoscopic fundoplication (**Option C**) or bariatric surgery for obesity, as well as magnetic sphincter augmentation (a magnetic ring is placed around the lower esophageal sphincter without surgical alteration of the stomach). Surgery is most effective in patients with typical symptoms of heartburn and regurgitation that respond to therapy. However, about one third of patients require resumption of a proton pump inhibitor 5 to 10 years after surgery. Postoperative complications include dysphagia, diarrhea, and inability to belch because of a tight fundoplication.

KEY POINT

- Men with gastroesophageal reflux disease symptoms for 5 years and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, intra-abdominal distribution of body fat, tobacco use) should be screened for Barrett esophagus.

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Item 18 Answer: A

Educational Objective: **Treat autoimmune hepatitis.**

The most appropriate management is continuation of immunosuppressant therapy (**Option A**). Autoimmune hepatitis is a chronic, inflammatory liver disease that has variable presentation, from asymptomatic elevation of aminotransferase levels to extrahepatic symptoms (e.g., myalgia and malaise) to acute liver failure. Diagnosis is based on laboratory test results, including the presence of antinuclear and smooth-muscle antibodies and elevated IgG levels, exclusion of other diagnoses (e.g., Wilson disease, viral hepatitis, and drug-induced liver injury), and liver biopsy. Patients with severe presentations require management by a hepatologist. The mainstay of treatment is immunosuppression. Induction of remission is typically with prednisone or a combination of prednisone and azathioprine. Depending on response, maintenance therapy may consist of prednisone or azathioprine monotherapy or combination therapy. Because of the high rate of relapse, therapy is recommended for at least 2 to 3 years. Biochemical response may occur within 3 to 8 months of treatment in 85% of patients whose disease responds to standard treatment, but histologic response can lag by several months. Therefore, a liver biopsy is recommended to demonstrate absence of active inflammation before cessation of therapy.

If the patient is doing well and aminotransferase levels have normalized, a biopsy is not necessary to monitor therapy (**Option B**). A biopsy is typically performed before attempted withdrawal of immunosuppressant therapy to assess risk for relapse. This patient has no indication for biopsy at this time.

Normalization of liver test results is insufficient to determine when it is safe to stop therapy. Stopping immunosuppressant therapy before completion of at least 2 years of therapy, regardless of aminotransferase levels, is associated with an increased risk for relapse. Therefore, stopping azathioprine therapy now and tapering prednisone (**Option C**) and stopping azathioprine now, tapering prednisone, and performing a liver biopsy (**Option D**) are not recommended. Because of the adverse effects of immunosuppressant therapy, indefinite treatment is avoided if possible. Some patients will require indefinite maintenance therapy because of relapsing disease. However, it is too soon to know whether this patient will remain in remission or relapse after discontinuation of immunosuppressant therapy.

KEY POINTS

- The mainstay of treatment of autoimmune hepatitis is immunosuppression with prednisone or a combination of prednisone and azathioprine.
- Because autoimmune hepatitis has a high rate of relapse, therapy is recommended for at least 2 to 3 years before discontinuation of the medications.

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Item 19 Answer: C

Educational Objective: **Diagnose colonic ischemia.**

The most likely diagnosis is colonic ischemia (**Option C**). This form of ischemic bowel disease is the most common and usually results from a nonocclusive low-flow state in microvessels. The term *colonic ischemia* is preferred to *ischemic colitis* because some patients do not have a documented inflammatory phase of disease. Risk factors for colonic ischemia include age (>60 years), female sex, vasoconstrictive and antihypertension medications, constipation, and thrombophilia. Colonic ischemia presents with abrupt onset of lower abdominal discomfort that is mild to moderate and cramping, followed within 24 hours by hematochezia (passage of fresh blood or clots from the colon). Physical examination usually reveals lower abdominal tenderness over the involved colonic segment without peritoneal signs. Leukocyte count and blood urea nitrogen may be mildly elevated. Abdominal CT is indicated to assess the severity, phase, and distribution of colonic ischemia. CT findings are nonspecific, including segmental bowel wall thickening and pericolonic fat stranding, often in the distribution of the "watershed" areas of the colon (splenic flexure and rectosigmoid junction). Colonoscopy is the primary method to diagnose colonic ischemia, usually after CT has shown a thickened segment of colon.

Acute diverticulitis (**Option A**) often presents with colicky lower abdominal pain and left-lower-quadrant abdominal tenderness on physical examination. However, acute diverticulitis does not present with rectal bleeding, making this diagnosis unlikely. In addition, CT scans in acute diverticulitis typically show pericolonic fat stranding of the sigmoid colon with associated diverticulosis, which is not seen on this patient's CT scan.

Clostridioides difficile infection (**Option B**) can mimic the presentation of colonic ischemia and must be excluded by stool tests. However, bloody diarrhea is uncommon in *C. difficile* colitis, and the infection often involves the colon in a diffuse fashion rather than the segmental pattern seen on this patient's CT scan.

Ulcerative colitis (**Option D**) can present with abdominal pain and bloody stools. However, it usually involves the rectum and extends proximally in a continuous and symmetric pattern. This patient's CT scan, showing segmental thickening of the descending and sigmoid colon with sparing of the rectum, makes ulcerative colitis unlikely, as do the abrupt symptom onset and older patient age.

KEY POINTS

- Colonic ischemia is the most common form of ischemic bowel disease and usually results from a nonocclusive low-flow state in microvessels.
- Colonic ischemia presents with abrupt-onset lower abdominal discomfort and cramping, followed within 24 hours by hematochezia.

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Item 20 Answer: A

Educational Objective: Treat ulcerative proctitis with topical 5-aminosalicylate.

The most appropriate treatment is a 5-aminosalicylate (5-ASA) suppository (**Option A**). Categories of the extent of ulcerative colitis include proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction), left-sided colitis (extending from the sigmoid to the splenic flexure), and extensive colitis (beyond the splenic flexure). This patient has findings consistent with mild ulcerative proctitis. Three factors must be considered in choosing therapy for ulcerative colitis: disease severity, distribution of disease, and previous therapies, including response and adherence. 5-ASAs are anti-inflammatory medications and the mainstay of treatment of mild to moderate ulcerative colitis. Patients with proctitis should receive topical therapy with 5-ASA suppositories. Patients with left-sided colitis should receive topical therapy with 5-ASA enemas. In mild to moderate left-sided or extensive ulcerative colitis, combined 5-ASA therapy (oral and topical) is superior for inducing remission compared with oral or topical therapies alone. Once remission is achieved, 5-ASAs are effective in maintaining it.

A glucocorticoid suppository (**Option B**) would be effective in inducing remission of ulcerative proctitis, but topical 5-ASA therapy is superior for this purpose. Topical glucocorticoid therapy may be considered in patients with disease limited to the rectum but intolerant of topical or oral 5-ASA therapy. In addition, 5-ASAs are effective in maintenance of remission, whereas topical glucocorticoids are effective only for induction.

Oral therapy with 5-ASA (**Option C**) would be less optimal than topical 5-ASA in this patient given the limited distribution of disease in the rectum. Oral 5-ASA would be an option if the patient declines use of a suppository.

Oral glucocorticoids (**Option D**) are commonly used to treat moderate to severe ulcerative colitis and are effective in inducing remission. However, given the significant adverse effects of glucocorticoids and the limited extent of disease in this patient, oral glucocorticoids would not be an appropriate treatment.

KEY POINTS

- Patients with ulcerative proctitis should receive topical therapy with 5-aminosalicylate suppositories; once remission is achieved, 5-aminosalicylates are effective in maintaining it.
- Combined 5-ASA therapy (oral and topical) is superior for inducing remission in patients with left-sided or extensive ulcerative colitis compared with oral or topical therapies alone.

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Item 21 Answer: C

Educational Objective: Diagnose hereditary hemochromatosis.

The most appropriate diagnostic test to perform next is transferrin saturation measurement (**Option C**). This patient's elevated ferritin level suggests a diagnosis of hereditary hemochromatosis, an autosomal recessive disorder of excessive accumulation of iron in the liver due to a mutation in the genes that control hepcidin synthesis. Cirrhosis and cardiomyopathy are major causes of morbidity; small-joint arthritis is common; and diabetes mellitus and other endocrinopathies may be seen. Early diagnosis may be made through evaluation of abnormal aminotransferase levels. In these patients, the diagnosis is suspected by finding elevated transferrin saturation greater than 45% (guidelines vary) and an elevated serum ferritin level; diagnosis is confirmed through genetic testing. Typically, patients have homozygosity of C282Y polymorphism of the *HFE* gene, but other polymorphisms, such as H63D, may be present.

α_1-Antitrypsin (AAT) (**Option A**) deficiency is an autosomal co-dominant genetic disorder that results in accumulation of a variant protein in the liver. Homozygosity for this condition may result in liver injury and eventual cirrhosis. The hepatic accumulation of AAT results in decreased circulating AAT, leading to lung disease. AAT deficiency does not cause elevations of serum ferritin.

MRI with special software is used to noninvasively assess the extent of cardiac and liver iron overload and generally obviates the need to perform organ biopsy to quantitate iron deposits. Liver biopsy (**Option B**) is used if it is also necessary to grade the degree of fibrosis or evaluate for other liver diseases. Liver biopsy is not indicated for this patient at this time and is not the appropriate next diagnostic test.

Porphyria cutanea tarda is diagnosed by plasma or urine porphyrin measurement (**Option D**). This disorder is a less common cause of secondary iron overload associated with acquired abnormalities in porphyrin metabolism and underlying liver disease, especially hepatitis C virus infection. Porphyria cutanea tarda is characterized by cutaneous blisters, often on the hands, and hypertrichosis. This patient has no findings of porphyria cutanea tarda.

KEY POINTS

- Hereditary hemochromatosis is suggested by the presence of an elevated serum ferritin level and transferrin saturation.
- The diagnosis of hereditary hemochromatosis is confirmed by testing for mutations in the *HFE* gene.

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Item 22 Answer: D

Educational Objective: Diagnose irritable bowel syndrome.

The most appropriate diagnostic test is stool testing for *Giardia* (**Option D**). The patient meets the clinical criteria for irritable bowel syndrome with abdominal pain at least 1 day a week for 3 months and at least two of the following: pain related to defecation, change in stool frequency, or change in stool consistency. IBS is a common cause of diarrhea and can be diagnosed on clinical grounds, including history and physical examination. Although an extensive workup for structural abnormalities is not indicated in the absence of alarm symptoms, fecal calprotectin testing to assess for inflammatory bowel disease and stool testing for giardiasis and celiac disease should be considered in patients with chronic diarrhea.

Abdominal ultrasonography (**Option A**) visualizes the gallbladder and biliary tree, and its role in the evaluation of abdominal pain is principally to exclude choledocholithiasis or biliary obstruction. Biliary colic pain is typically postprandial, particularly after fatty meals. Diarrhea is not a feature of biliary colic. Given the patient's symptoms, ultrasonography is not indicated.

Colonoscopy with biopsy of the right and left colon (**Option B**) is performed to investigate for microscopic colitis, a form of inflammatory bowel disease that most commonly affects women in the seventh or eighth decades of life. It is characterized by watery diarrhea and is sometimes associated with medication use, including NSAIDs. Microscopic colitis does not have to be ruled out in a patient meeting clinical criteria for IBS without alarm symptoms.

Escherichia coli O157:H7 (**Option C**) can cause acute inflammatory diarrhea via toxin-mediated injury to the colon. Clinical manifestations include bloody diarrhea, tenesmus, and leukocytosis. This condition can progress to hemolytic uremic syndrome. The chronic time course and nonbloody nature of diarrhea in this patient make this diagnosis unlikely.

KEY POINTS

- The diagnosis of irritable bowel syndrome requires symptoms of recurrent abdominal pain at least 1 day a week for 3 months, along with at least two of the following: pain related to defecation, change in stool frequency, or change in stool consistency.
- Fecal calprotectin testing to assess for inflammatory bowel disease and stool testing for giardiasis and celiac disease should be considered in patients with chronic diarrhea.

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Item 23 Answer: C

H

Educational Objective: Evaluate unstable lower gastrointestinal bleeding.

The most appropriate next diagnostic test is CT angiography (CTA) (**Option C**). This patient has active lower gastrointestinal bleeding with associated hemodynamic instability. In addition to continued intravenous fluid resuscitation, rapid identification of the bleeding source is essential. CTA is the study of choice in this setting because it can be performed quickly and has the greatest likelihood of localizing the site of bleeding (with an accuracy of nearly 100%). CTA can detect bleeding at a rate of 0.3 mL/min.

Although conventional angiography (**Option A**) allows transarterial embolization at time of diagnosis, it is limited by the need for a higher rate of bleeding (0.5-1.0 mL/min) than that for CTA to identify a bleeding source. Complications of conventional angiography, including acute kidney injury and thromboembolic events, have been reported in up to 10% of case series. Catheter angiography and possible embolization should be performed as soon as possible after a positive CTA finding.

In hemodynamically stable patients without evidence of rapid bleeding, colonoscopy (**Option B**) is the first study of choice in patients with lower gastrointestinal bleeding. It should be performed within 24 hours of presentation after adequate colon preparation. Colonoscopy identifies a source of bleeding in two thirds of patients.

Upper endoscopy (**Option D**) should be performed immediately if no bleeding source is identified by initial CTA. Upper endoscopy may be the first procedure performed if suspicion for upper gastrointestinal bleeding is high. Upper gastrointestinal bleeding is a consideration in this patient taking aspirin and an NSAID. However, the presence of bilious fluid without blood following nasogastric tube lavage suggests that the pylorus is open and there is no active upper gastrointestinal bleeding proximal to the ligament of Treitz. In this patient, CTA is the preferred initial diagnostic test.

KEY POINTS

- For active lower gastrointestinal bleeding with associated hemodynamic instability, CT angiography is the study of choice.
- For active lower gastrointestinal bleeding, catheter angiography and possible embolization should be performed as soon as possible after positive results on CT angiography.

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Item 24 Answer: A

Educational Objective: Evaluate gastric varices in a patient with cirrhosis.

The most appropriate next step in management is abdominal CT with contrast (**Option A**). Gastric varices occur in up to 20% of patients with cirrhosis and can be challenging to manage. Typically, octreotide is administered to reduce portal pressures, and antibiotics are provided to reduce risk for infectious complications of gastrointestinal bleeding. These complications include bacteremia, which can increase morbidity and mortality from variceal bleeding. Treatment options for gastric varices along the greater curvature of the stomach depend on the anatomy of the abdominal vasculature. For isolated gastric varices due to splenic vein thrombosis, splenectomy can be performed to decompress varices. If the portal vein is patent and a suitable splenorenal shunt is available, balloon-occluded retrograde transvenous obliteration of varices can be considered. If the anatomy of the hepatic veins and portal vein branches is favorable, a transjugular intrahepatic portosystemic shunt may be an option. To determine the best therapy, contrast-enhanced cross-sectional imaging is required. Therefore, abdominal CT with contrast is the best next action.

Gastric fundal varices are much more frequent in patients with portal vein and/or splenic vein thrombosis, and the finding of these varices should prompt cross-sectional imaging to investigate the presence of such thromboses. Endovascular obliteration is an option in patients with a large gastro- or splenorenal collateral; therefore, cross-sectional vascular imaging with contrast-enhanced CT is preferred over abdominal ultrasonography (**Option B**) because it would investigate both thrombosis and the presence of such collaterals and would guide management accordingly.

Balloon tamponade (**Option C**) provides only short-term tamponade of bleeding varices. It is best used in unstable patients as a temporizing device while more definitive therapy is pending. In this hemodynamically stable patient, balloon tamponade is not necessary.

Band ligation (**Option D**) is an effective therapy for esophageal varices, as well as varices in the gastric cardia, which extend from the esophagus into the lesser curvature of the stomach. Band ligation is effective in these types of varices because of their predictable anatomy and more superficial location, which permits thorough eradication. In this patient, band ligation is not a good option because varices in the gastric fundus are not amenable to this approach.

KEY POINT

- In patients with gastric varices, contrast-enhanced cross-sectional imaging should be performed to determine the best treatment.

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Item 25 Answer: A

Educational Objective: Treat colon cancer in patient with familial adenomatous polyposis.

The most appropriate treatment is colectomy (**Option A**). This patient likely has a de novo mutation in the *APC* gene causing familial adenomatous polyposis (FAP). Classic FAP is characterized by more than 100 adenomatous polyps in the colon, and lifetime risk for colon cancer approaches 100%. Other intestinal manifestations of FAP include benign fundic gland polyps of the stomach, duodenal adenomas, and ampullary adenomas. Extracolonic manifestations include desmoid tumors, papillary thyroid cancer, extra teeth, cysts, osteomas, and congenital hypertrophy of the retinal pigmented epithelium. De novo mutations are found in up to 25% of FAP cases. The patient should undergo genetic counseling and germline genetic testing, which would confirm a diagnosis of FAP. Her unaffected parents should also undergo genetic testing to confirm that this finding is a de novo mutation. If her parents have FAP, they should undergo upper endoscopy with a side-viewing endoscope (duodenoscope), colonoscopy, and thyroid ultrasonography. Because mutations in *APC* behave in an autosomal dominant fashion, each child of an affected individual should be counseled that they have a 50% chance of inheriting the *APC* mutation. The timing of genetic testing for offspring can be discussed with providers, but sigmoidoscopy or colonoscopy should begin at ages 10 to 12 years. If adenomas are detected, even children who have not had genetic testing should be screened as if they have a confirmed mutation. The treatment of choice in FAP is colectomy. The surgical approach depends on the rectal polyp burden. In this patient, the rectum is relatively spared, and the patient may be a candidate for a subtotal colectomy with sparing of the rectum. Following colectomy, she should have annual sigmoidoscopy, as well as surveillance of her upper gastrointestinal tract and thyroid.

Endoscopic removal of the adenocarcinoma (**Option B**) is not recommended because it would not provide adequate lymph node sampling and would leave the remaining colon at risk for future cancers.

Left hemicolectomy (**Option C**) may be considered for sporadic colon cancer but not for FAP because of the increased cancer risk in the remaining colon.

Sulindac (**Option D**) is an NSAID that may be considered to reduce rectal polyp burden after surgery or as chemoprevention in addition to endoscopic management of colon polyps. It is not appropriate therapy for colon cancer.

KEY POINT

- The treatment of choice in familial adenomatous polyposis is colectomy.

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Item 26 Answer: B

Educational Objective: Treat hepatocellular carcinoma with surgical resection.

The most appropriate management is surgical resection (**Option B**). Patients with hepatocellular carcinoma who have well-compensated cirrhosis, no symptoms referable to liver disease, no evidence of portal hypertension, and normal liver function markers, like this patient, typically can tolerate surgical resection. The left liver is smaller than the right liver; therefore, in this patient, resection of cancer that spares the right liver should be undertaken. Screening for hepatocellular carcinoma is important in patients with cirrhosis, even those who have undergone successful antiviral therapy for hepatitis C virus infection. Although successful antiviral therapy decreases the risk for hepatocellular carcinoma, the risk is not eliminated and screening with abdominal ultrasonography should be performed indefinitely at 6-month intervals. Patients who undergo surgical resection are at risk for recurrent hepatocellular cancer, and surveillance imaging should continue after resection.

Liver transplantation (**Option A**) for hepatocellular cancer is the best therapy for patients who also have portal hypertension or features of liver dysfunction, such as jaundice, and cannot undergo liver resection. This patient has well-compensated cirrhosis and should be referred for resection rather than liver transplantation.

Liver-directed cytoreductive therapies, including transarterial chemoembolization (**Option C**), transarterial radioembolization, stereotactic body radiotherapy, and radiofrequency ablation, are considered when patients are not candidates for surgical resection or liver transplantation. These locoregional procedures typically decrease the size of liver tumors and may be curative, but they are not as definitive as resection and thus are considered second-line therapies. This patient is a candidate for surgical resection as first-line therapy.

Ongoing surveillance (**Option D**) is not appropriate in a patient who can be considered for resection of hepatocellular carcinoma. The only potential role for ongoing surveillance of this condition is for a suspected lesion being monitored for growth at short intervals in the context of potential liver transplantation. In this patient with potentially resectable hepatocellular carcinoma, surveillance is not warranted.

KEY POINTS

- Patients with hepatocellular carcinoma who have well-compensated cirrhosis, no symptoms referable to liver disease, no evidence of portal hypertension, and normal liver function markers should be referred for surgical resection.
- Liver transplantation for hepatocellular cancer is the best therapy for patients who also have portal hypertension or features of liver dysfunction.

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Item 27 Answer: C

Educational Objective: Diagnose small-duct primary sclerosing cholangitis.

The most appropriate next step in management is liver biopsy (**Option C**). Primary sclerosing cholangitis (PSC) is an autoimmune fibroinflammatory disease of the intrahepatic bile ducts; it most commonly affects the large ducts but can also affect the small intrahepatic ducts. It is associated with inflammatory bowel disease in about 85% of cases and occurs in approximately 7.5% of patients with ulcerative colitis. PSC can be diagnosed with magnetic resonance cholangiopancreatography (MRCP). Although a liver biopsy is rarely needed to diagnose PSC, diagnosis of small-duct PSC requires a liver biopsy. In this patient at risk for sclerosing cholangitis, with liver enzyme levels indicating cholestatic liver disease and a normal MRCP result, a liver biopsy should be performed to evaluate for small-duct PSC.

Drug-induced liver injury encompasses a spectrum of liver injury and can be induced by many medications. This patient demonstrates cholestatic injury characterized by a disproportionate elevation in the alkaline phosphatase level compared with serum aminotransferase levels. Levofloxacin is more commonly associated with a hepatocellular pattern of injury characterized primarily by elevations of aminotransferase levels. More importantly, the cholestatic pattern of liver injury was discovered before initiation of levofloxacin, strongly suggesting another cause for the patient's liver injury. Therefore, discontinuation of levofloxacin (**Option A**) is not necessary.

In patients with sclerosing cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) (**Option B**) can be used to dilate strictures and remove stones in symptomatic patients with jaundice and pruritus or bacterial cholangitis. ERCP can also be performed after MRCP to investigate a bile duct mass. This patient does not have indications for ERCP.

Liver ultrasonography (**Option D**) can be useful in the initial evaluation of cholestasis. The presence of biliary dilatation on ultrasonography indicates gallstones, strictures, or malignancy, whereas the absence of biliary dilatation is compatible with intrahepatic cholestasis. In this patient with ulcerative colitis and a pattern of cholestatic injury, MRCP was appropriately performed and had normal results. MRCP is more sensitive in the diagnosis of sclerosing cholangitis than is ultrasonography. Liver ultrasonography will not provide any additional useful information. The most helpful diagnostic test will be a liver biopsy.

KEY POINTS

- Primary sclerosing cholangitis is an autoimmune fibroinflammatory disease that most commonly affects the large bile ducts but can also affect the small intrahepatic ducts; it can be diagnosed with magnetic resonance cholangiopancreatography.
- Liver biopsy is needed to diagnose small-duct primary sclerosing cholangitis.

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Item 28 Answer: B

Educational Objective: **Provide appropriate health care maintenance in a patient with inflammatory bowel disease.**

The most appropriate health maintenance screening to perform is cervical cancer screening (**Option B**). Patients with inflammatory bowel disease (IBD) have increased risk for colorectal, cervical, and skin cancers. The U.S. Preventive Services Task Force recommends screening women aged 21 to 65 years every 3 years with cytology (Pap test). In women aged 30 to 65 years who want to extend the screening interval, high-risk human papillomavirus (HPV) testing (preferred) or cytology combined with high-risk HPV testing can be performed every 5 years. However, women with IBD have increased risk for cervical dysplasia; this risk is greater in women using immunosuppressive therapy. Women with IBD receiving immunosuppressive therapy should undergo Pap testing annually. Patients with IBD also have increased risk for vaccine-preventable illnesses. Inactivated vaccines can be safely administered to all patients with IBD, regardless of immunosuppression. Depression and anxiety are more common in patients with IBD than in the general population, and screening is recommended. Patients with ulcerative colitis and Crohn disease should undergo yearly melanoma screening, and those receiving immunomodulators should be screened for nonmelanoma squamous cell cancer while using these agents.

Evidence is insufficient to recommend routine anal cancer screening (**Option A**) in average-risk populations, but such screening may be considered in high-risk populations. The Infectious Diseases Society of America suggests screening patients with genital warts, men who have sex with men, and women who have a history of abnormal cervical cytology results or participate in receptive anal intercourse. The presence of IBD is not an indication to routinely screen for anal cancer.

Patients with IBD are at increased risk for colorectal cancer through longstanding colorectal inflammation. In patients who have ulcerative colitis with disease proximal to the sigmoid colon or Crohn disease with more than one third of the colon involved, surveillance colonoscopy (**Option C**) should be done 8 years after diagnosis and then every 1 to 2 years thereafter. Because this patient has had IBD for only 2 years, surveillance colonoscopy is not yet necessary.

Patients with IBD also have elevated risk for metabolic bone disease through use of glucocorticoids and diminished vitamin D and calcium absorption. Bone mineral density testing with dual-energy x-ray absorptiometry (**Option D**) is recommended in all patients starting oral glucocorticoid therapy. Otherwise, patients with IBD should be screened for osteoporosis on the basis of established guidelines for the general population. Performing dual-energy x-ray absorptiometry in this patient is not indicated because she is not starting glucocorticoid therapy and has no conventional risk factors for osteoporosis.

KEY POINT

- Women with inflammatory bowel disease receiving immunosuppressive therapy should undergo Pap testing annually.

Bibliography

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Item 29 Answer: B

Educational Objective: **Diagnose eosinophilic esophagitis.**

The most likely diagnosis is eosinophilic esophagitis (EoE) (**Option B**). This patient presented with a food impaction that resolved spontaneously. Most patients with EoE are men diagnosed between the second and fifth decades of life, and many have other atopic conditions, such as asthma, rhinitis, dermatitis, and seasonal or food allergies. The diagnostic criteria for EoE are symptoms of esophageal dysfunction, esophageal biopsy specimens showing persistent eosinophil counts of at least 15/hpf, and exclusion of other causes of eosinophilia. Examples of other causes of esophageal eosinophilia include gastroesophageal reflux disease, hypereosinophilic syndrome, infections (i.e., fungal, viral), autoimmune and connective tissue disorders, Crohn disease with esophageal involvement, and drug hypersensitivity reactions. Peripheral eosinophilia is not a diagnostic criterion for EoE. Upper endoscopy with biopsies to confirm this diagnosis is appropriate. Treatment options include a proton pump inhibitor, swallowed topical glucocorticoids (e.g., fluticasone, budesonide), and/or endoscopic dilation. An empiric elimination diet may help treat and prevent flares in EoE.

Barrett esophagus (**Option A**) is a complication of chronic acid reflux disease and is a risk factor for esophageal cancer. However, it does not cause dysphagia with food impaction.

Although esophageal cancer (**Option C**) can cause solid food dysphagia in older patients, it is often persistent and progressive but not intermittent with spontaneous resolution as seen in this young patient.

Patients with symptomatic peptic strictures (**Option D**) often have long-standing reflux or heartburn, which are not present in this patient.

Symptoms of esophageal dysmotility and reflux are common in all forms of systemic sclerosis (**Option E**). Dysphagia is the result of incomplete peristalsis, and reflux results from decreased lower esophageal sphincter pressure. Patients with systemic sclerosis usually have associated skin findings and sclerodactyly. This patient lacks these characteristics.

KEY POINTS

- Eosinophilic esophagitis is a condition commonly associated with dysphagia and food bolus obstruction, usually found in younger men with atopic conditions.
- Diagnostic criteria for eosinophilic esophagitis are dysphagia, esophageal biopsy specimens with eosinophil counts of at least 15/hpf, and exclusion of other causes of eosinophilia.

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Item 30 Answer: C

Educational Objective: Screen for hepatocellular carcinoma in a patient with cirrhosis.

The most appropriate surveillance modality for hepatocellular carcinoma (HCC) is ultrasonography of the liver (**Option C**) every 6 months. Adults with cirrhosis are at the highest risk for HCC and should undergo surveillance regardless of the cause of cirrhosis. In most patients with hepatitis C virus (HCV) infection, cure rates seen with direct-acting antiviral agents exceed 90%. Sustained virologic response is defined as a negative HCV RNA result 12 weeks after therapy and defines virologic cure. Virologic cure is associated with reduced risk for progression to cirrhosis, cirrhosis complications, hepatocellular carcinoma, and liver-related mortality. The risk for HCC in patients with HCV-related cirrhosis who achieve virologic cure after antiviral treatment is lowered, but not eliminated; therefore, patients with cirrhosis and treated HCV infection should undergo surveillance for HCC every 6 months. The addition of α-fetoprotein (AFP) measurement to ultrasonography increases the sensitivity of HCC detection but also increases the false-positive rate. No available information indicates that the addition of AFP measurement to biannual ultrasonography leads to improved survival. Therefore, the American Association for the Study of Liver Disease (AASLD) recommends surveillance using ultrasonography with or without AFP every 6 months.

The AASLD does not recommend MRI (**Option A**) or CT (**Option B**) as the primary modality for the surveillance of HCC in patients with cirrhosis. Although these modalities are more sensitive than ultrasonography, there is no evidence that this translates to improved survival. However, the AASLD notes that in select patients with a high likelihood of having an inadequate ultrasound or in whom ultrasonography is attempted but inadequate, MRI or CT may be used.

No surveillance (**Option D**) is inappropriate because patients with cirrhosis, such as this patient, are at increased risk for HCC. The AASLD recommends surveillance of adults with cirrhosis because it improves overall survival.

KEY POINTS

- Patients with cirrhosis who have undergone virologic cure for hepatitis C virus infection should undergo surveillance for hepatocellular carcinoma every 6 months with ultrasonography.
- No information indicates that the addition of α-fetoprotein (AFP) to ultrasonography screening for hepatocellular carcinoma leads to improved survival; therefore, surveillance using ultrasonography may be performed with or without AFP measurement every 6 months.

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Item 31 Answer: D

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Educational Objective: Manage narcotic bowel syndrome.

The most appropriate management is opioid discontinuation (**Option D**). The patient has progressively severe abdominal pain that requires escalating narcotic doses. The paradoxical worsening of her pain despite dose escalation is consistent with narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia. The proposed cause of narcotic bowel syndrome is centrally mediated opioid-induced hyperalgesia, but the pathophysiological mechanism is not well defined. The condition is characterized by a patient's fear of tapering narcotics; however, the only effective treatment is complete cessation of narcotic use, which is most successfully achieved in a supervised detoxification program. During the detoxification process, nonpharmacologic therapies, such as stress reduction and exercise, are introduced and adjuvant

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treatments with nonopioid analgesics, such as antidepressants, are added. Psychotherapy may be beneficial.

Lubiprostone (**Option A**) activates type 2 chloride channels on enterocytes lining the gut lumen, causing chloride ions to move into the colonic lumen with sodium and water following the ionic gradient. It is used to treat constipation-predominant irritable bowel syndrome and chronic idiopathic constipation. Lubiprostone is not indicated because this patient's constipation is controlled with polyethylene glycol and her symptoms are not likely related to irritable bowel syndrome.

Methadone (**Option B**), an opiate with a long half-life, is used for management of chronic pain or maintenance therapy for opiate abuse. Because pain in narcotic bowel syndrome worsens with continued or escalating opiate dosing and can be treated only by discontinuing opiate use, methadone is not an effective treatment in this condition.

Colonoscopy with biopsy (**Option C**) of the right and left colon is performed to assess for microscopic colitis, a form of inflammatory bowel disease that causes watery diarrhea. Although abdominal pain can be present in patients with microscopic colitis, this patient's history of constipation treated with polyethylene glycol make this diagnosis unlikely.

KEY POINT

- Narcotic bowel syndrome is characterized by paradoxical worsening of abdominal pain despite dose escalation; complete cessation of narcotic use is the only effective treatment.

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Item 32 Answer: E

Educational Objective: Manage asymptomatic pancreatic pseudocysts.

The most appropriate management is observation (**Option E**). This patient has recovered from alcohol-induced pancreatitis and now has a pancreatic pseudocyst. Pancreatic pseudocysts are one of the four types of fluid collections seen in acute pancreatitis; the others are acute peripancreatic fluid collections, acute necrotic collections, and walled-off necrosis. Pancreatic pseudocysts are defined as peripancreatic fluid collections that persist beyond 4 weeks. They develop a well-defined wall, but this wall lacks the epithelial layer required of a true cyst. Pseudocysts do not contain solid material or debris and do not require drainage unless the patient is symptomatic or the pseudocysts become infected. This patient feels well and thus does not require drainage. Ongoing expectant management and observation are appropriate.

Acute necrotic collections are areas of pancreatic necrosis that develop within the first 4 weeks of acute pancreatitis. Necrosis may occur within the pancreatic parenchyma or in the peripancreatic tissues. Walled-off necrosis occurs when necrotic areas liquefy and become encapsulated with a well-defined wall surrounding the necrotic area. Because of the semi-solid nature of the debris in walled-off necrosis, these lesions are not typically amenable to simple endoscopic needle drainage and may require endoscopic drainage, such as endoscopic cystogastrostomy and necrosectomy (**Option A**), or surgical drainage. Because this patient has a pseudocyst, he does not require these procedures.

Endoscopic retrograde pancreatography (**Option B**) is not recommended for pancreatic fluid collections. Instrumentation of the pancreatic duct carries a risk for pancreatitis. Although this procedure may provide information, such as connection of the fluid collection to the pancreatic duct, this information will not change management. Therefore, the procedure is not appropriate for this patient.

If a patient is symptomatic or there is concern for infection, endoscopic ultrasonography with fine-needle aspiration (**Option C**) can be considered. For symptomatic pancreatic pseudocysts, endoscopic drainage is preferred over surgical drainage (**Option D**) given its lesser morbidity. This patient is asymptomatic and thus does not need to undergo ultrasonography and fine-needle aspiration.

KEY POINTS

- Pancreatic pseudocysts are peripancreatic fluid collections that occur with acute pancreatitis and do not contain solid material or debris.
- Pancreatic pseudocysts do not require drainage unless the patient is symptomatic or the pseudocysts become infected.

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Item 33 Answer: B

Educational Objective: Diagnose acute mesenteric ischemia.

The most appropriate diagnostic test to perform next is CT angiography (**Option B**). This patient has acute mesenteric ischemia (AMI) caused by an abrupt decrease in blood flow to the small intestine, likely due to an embolus related to atrial fibrillation. AMI most commonly presents with abrupt onset of severe periumbilical abdominal pain followed by the urge to defecate. Although the patient reports severe abdominal pain, physical examination reveals a soft, nontender, nondistended abdomen without peritoneal signs. Pain that is disproportionate to physical examination findings should immediately raise suspicion for early AMI. With late presentation, intestinal ischemia progresses to infarction and peritoneal signs develop. This late presentation of AMI is associated with a high mortality rate. Results of laboratory studies and abdominal imaging in early AMI are nonspecific. Most patients will have an elevated leukocyte count. Serum lactate level may be

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normal and does not exclude the diagnosis. CT angiography is the recommended imaging modality to diagnose AMI.

Colonoscopy with biopsy (**Option A**) is the test of choice to confirm the diagnosis of colonic ischemia. This ischemia presents with the abrupt onset of lower abdominal discomfort that is mild to moderate and cramping, followed within 24 hours by hematochezia (passage of fresh blood or clots from the colon). This patient's presentation is not consistent with colonic ischemia, and colonoscopy is not indicated.

Doppler ultrasonography (**Option C**) is an effective, low-cost method to assess the proximal mesenteric vessels. However, adequate ultrasonography often cannot be performed in patients with AMI, making it an inferior option to CT angiography.

Although magnetic resonance angiography (**Option D**) avoids the risks of radiation and contrast exposure, it takes longer and is less sensitive for distal and nonocclusive disease in patients suspected of having AMI.

KEY POINTS

- Early acute mesenteric ischemia most commonly presents with abrupt onset of severe periumbilical abdominal pain followed by the urge to defecate and an unremarkable abdominal examination.
- CT angiography is the recommended imaging modality for the diagnosis of acute mesenteric ischemia.

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Item 34 Answer: C

Educational Objective: Diagnose medication-induced chronic diarrhea.

The most likely cause of this patient's diarrhea is metformin (**Option C**). The patient reports a 4-month history of diarrhea characterized by watery, nonbloody bowel movements. This duration of symptoms (>4 weeks) is classified as chronic diarrhea. In contrast to acute diarrhea, which is usually caused by infectious agents, chronic diarrhea is more commonly noninfectious. Patients with diarrhea should be asked about new medications and the timing of the initiation of medication in relation to diarrhea onset. Metformin is a common cause of chronic watery diarrhea, possibly related to a promotility effect and stimulation of intestinal chloride secretion. The temporal association with the commencement of metformin (which was started 4 months ago, coinciding with symptom onset) strongly suggests that metformin is the cause of diarrhea.

Although *Clostridioides difficile* colitis (**Option A**) can result from antibiotic use, the time between amoxicillin use and onset of diarrhea argues against amoxicillin as the triggering event.

Crohn disease (**Option B**) can cause watery diarrhea or inflammatory diarrhea. However, it is less likely than metformin to have triggered the patient's symptoms given the temporal relationship between symptom onset and commencement of metformin. Moreover, the normal erythrocyte sedimentation rate and lack of abdominal pain or tenderness on physical examination argue against Crohn disease.

Microscopic colitis (**Option D**) is a distinct type of inflammatory bowel disease characterized by macroscopically normal mucosa with inflammatory changes seen on histopathology of colon biopsy specimens. It is subclassified into lymphocytic colitis and collagenous colitis on the basis of predominating histologic features. Microscopic colitis predominantly affects middle-aged women. Medications, including NSAIDs, selective serotonin reuptake inhibitors, and proton pump inhibitors, have been associated with the development of microscopic colitis.

KEY POINTS

- Acute diarrhea is usually caused by infectious agents, whereas chronic diarrhea is more commonly noninfectious.
- Patients with chronic diarrhea should be asked about new medications and the timing of the initiation of medication in relation to the onset of diarrhea; metformin is a common cause of chronic watery diarrhea.

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Item 35 Answer: D

Educational Objective: Treat nonalcoholic fatty liver disease.

The most appropriate next step in management is weight loss (**Option D**). This patient likely has nonalcoholic fatty liver disease (NAFLD) given the presence of diabetes, obesity, hypertension, and hyperlipidemia. Diabetes is associated with the development of NAFLD, including its more severe manifestations of nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma. Elevations of hepatic aminotransferase concentrations are associated with higher BMI, waist circumference, and triglyceride levels and lower HDL cholesterol levels. Patients with type 2 diabetes or prediabetes and elevated liver enzyme levels or fatty liver on ultrasound should be evaluated for presence of NASH and liver fibrosis. Noninvasive tests, such as elastography or fibrosis biomarkers, may be used to assess risk for fibrosis, but referral to a liver specialist and liver biopsy may be required for definitive diagnosis. The mainstay of NAFLD management is weight loss. Weight loss of at least 5% improves steatosis, whereas weight loss of 8% to 10% improves steatohepatitis and fibrosis. No specific diet for NAFLD is recommended. Bariatric surgery and concomitant weight loss improve inflammation and fibrosis associated with NAFLD.

This patient does not excessively use alcohol, so alcohol cessation (**Option A**) is unlikely to resolve his steatosis. No amount of alcohol use is safe in patients with liver disease.

Statins are safe in most patients with NAFLD and should not be discontinued (**Option B**). Cardiovascular disease is the leading cause of death in patients with NAFLD, and initiation of therapy with statins should be considered in patients with NALD at high risk for cardiovascular events. There is no relationship between statin use and steatosis in NAFLD.

No drugs have been approved by the FDA for the treatment of NAFLD. Pioglitazone (**Option C**) and vitamin E treatment of biopsy-proven nonalcoholic steatohepatitis improve liver histology, but effects on longer-term clinical outcomes are not known and routine use for NAFLD is not recommended.

KEY POINTS

- Patients with type 2 diabetes or prediabetes and elevated liver enzymes or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis.
- The mainstay of management of nonalcoholic fatty liver disease is weight loss.

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Item 36 Answer: A

Educational Objective: Treat the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.

The most appropriate management is delivery of the fetus (**Option A**). The third trimester of pregnancy can be complicated by potentially serious liver conditions. The HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome is a serious manifestation of preeclampsia and must be recognized promptly. HELLP typically presents with nonspecific symptoms, such as abdominal pain, nausea with vomiting, pruritus, and jaundice. The only definitive therapy is delivery of the fetus. Prompt treatment is paramount because rates of fetal and maternal mortality are high. Treatment with first-line agents for severe hypertension should occur as soon as possible to reduce the risk for maternal stroke. The goal is to rapidly achieve a blood pressure in the range of 140 to 150/90 to 100 mm Hg. Coagulopathy may increase the risk for bleeding in the perinatal state. Liver dysfunction can worsen in the 48 hours after delivery before resolving. Rarely, liver transplantation may be required if symptoms of liver failure progress.

Thrombotic thrombocytopenic (TTP) is characterized by microangiopathic hemolytic anemia and thrombocytopenia. Acquired TTP is caused by a deficiency in the metalloprotease ADAMTS13, which is responsible for cleaving high-molecular-weight von Willebrand factor multimers. These multimers accumulate, generating platelet-rich thrombi in small vessels. Initial treatment involves therapeutic plasma exchange (**Option B**) to remove the multimers and replace the deficient ADAMTS13. Although this patient has hemolytic anemia and thrombocytopenia, a third-trimester pregnancy and elevated liver enzyme levels are more compatible with HELLP syndrome.

If bleeding is not controlled, or if an invasive procedure is planned, transfusion of platelets (**Option C**) or plasma may be warranted. In the absence of bleeding, as in this patient, administration of platelets is not necessary. Any intervention that delays delivery of the fetus should be avoided.

Intrahepatic cholestasis of pregnancy can develop during earlier stages of pregnancy and causes pruritus. Potential complications include premature labor and fetal death. Although ursodeoxycholic acid (**Option D**) can be helpful in intrahepatic cholestasis of pregnancy, it has no benefit in the HELLP syndrome and therefore is not an appropriate choice for this patient.

KEY POINTS

- The HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome typically presents with nonspecific symptoms, such as abdominal pain, nausea with vomiting, pruritus, and jaundice.
- The HELLP syndrome is treated by prompt delivery of the fetus.

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Item 37 Answer: D

Educational Objective: Manage lactase deficiency.

The most appropriate management is a trial of a lactose-free diet (**Option D**). The patient describes diarrhea lasting longer than 4 weeks, thereby meeting the criteria for chronic diarrhea. The lack of nocturnal symptoms and improvement of symptoms with fasting suggest osmotic diarrhea. Osmotic diarrhea results from a nonabsorbed, osmotically active substance in the intestinal lumen, leading to luminal fluid accumulation due to an osmotic gradient. This gradient is present after ingestion of an osmotically active substance and is absent during fasting (including during sleep). A common cause of osmotic diarrhea is lactase deficiency that results in lactose malabsorption, which typically presents in young adulthood. In this condition, brush-border lactase is lost and ingested lactose is no longer broken down to its constituent monosaccharides. The persistent presence of this unabsorbed disaccharide creates an osmotic gradient. Although a lactose breath test is available to test for lactase deficiency, the diagnosis can typically be based on improvement after exclusion of dietary lactose or administration of lactase enzymes with meals.

Colonoscopy (**Option A**) has a role in the evaluation of chronic diarrhea: to diagnose inflammatory bowel disease (IBD) or, along with colonic biopsies, microscopic colitis. Although IBD is a cause of chronic diarrhea, it is less common than lactase deficiency. In addition, this patient's lack of weight loss, anemia, and negative fecal calprotectin result make IBD an unlikely diagnosis. Thus, colonoscopy is not necessary.

Fructose (**Option B**), a monosaccharide found in fruit and as an added sweetener in processed foods, is absorbed via a fructose transporter on the luminal surface of enterocytes (epithelial cells of the small intestine). Defects in this transporter can lead to fructose malabsorption, and osmotic diarrhea may ensue. Fructose intolerance is less common than lactase deficiency and is a controversial diagnosis. Empiric treatment for lactose malabsorption, a well-established and common diagnosis, is the most reasonable initial management for this patient.

Stool culture (**Option C**) may be performed in the setting of diarrhea due to a suspected bacterial cause, such as *Escherichia coli* or *Campylobacter jejuni*. These infections typically cause acute diarrhea, not the chronic diarrhea seen in this patient.

KEY POINTS

- The most common cause of osmotic diarrhea is lactase deficiency that results in lactose malabsorption.
- Lactase deficiency can be diagnosed on the basis of improvement after exclusion of dietary lactose or administration of lactase enzymes with meals.

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Item 38 Answer: A

Educational Objective: Manage renal dysfunction in a patient with cirrhosis.

The most appropriate initial management is discontinuation of diuretics (**Option A**). In a patient with cirrhosis and portal hypertension, ascites is a manifestation of inadequate natriuresis, with increased splanchnic blood flow and reduced renal perfusion. These factors contribute to accumulation of fluid in the peritoneal space. Initial management of ascites includes dietary sodium restriction and diuretic therapy with spironolactone and furosemide. As the splanchnic vasculature progressively dilates and renal perfusion decreases with worsening of portal hypertension, hepatorenal syndrome can develop, which manifests as declining renal function. The initial evaluation of these patients is investigation for a decrease in intravascular volume and for infection and exclusion of other causes of acute kidney injury. In this patient, furosemide and spironolactone may be exacerbating renal hypoperfusion and should be stopped. Assessment for oliguria, urinalysis (bland urinary sediment), and urine sodium concentration (low) is also appropriate in the evaluation for suspected hepatorenal syndrome.

Fluid restriction (**Option B**) can be useful in patients who develop dilutional, hypervolemic hyponatremia. Although this patient is hypervolemic, she does not have hyponatremia; she has impaired natriuresis and requires dietary sodium restriction, not fluid restriction.

Nonselective β-blockers, such as propranolol (**Option C**), are often used in patients with cirrhosis and portal hypertension to decrease portal pressures and reduce risk for variceal hemorrhage. However, in the setting of refractory ascites or hepatorenal syndrome, β-blocker therapy should not be initiated because it can lower renal perfusion pressures and worsen clinical outcomes. β-Blockers that are already a part of a patient's medication regimen should be discontinued in this context.

This hypervolemic patient already has excessive total-body sodium, and liberalizing dietary sodium intake (**Option D**) would not be expected to improve clinical outcomes. Rather, an increase in dietary sodium intake would worsen volume overload yet not necessarily improve renal function.

KEY POINTS

- The initial management of acute kidney injury in patients with cirrhosis is to stop diuretic therapy.
- In patients with hepatorenal syndrome, β-blocker therapy should be discontinued.

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Item 39 Answer: C

Educational Objective: Treat spontaneous bacterial peritonitis.

The most appropriate initial treatment is intravenous albumin and a third-generation cephalosporin, such as cefotaxime (**Option C**). Spontaneous bacterial peritonitis (SBP) is an infection of ascitic fluid in patients with portal hypertension. SBP can present with fever, abdominal pain, and/or kidney dysfunction; it should be considered in any patient with ascites whose status declines. SBP is diagnosed by an ascitic fluid neutrophil count of 250/µL (0.25×10^9/L) or greater. Bacterial culture of ascitic fluid should also be performed but is often negative. Initial treatment of SBP entails prompt initiation of a third-generation cephalosporin and adjunctive albumin therapy. Such treatment has a survival benefit. SBP has a high mortality rate, and patients who develop SBP should be considered for liver transplantation.

In patients with cirrhosis and ascites, long-term prophylactic antibiotic therapy, typically with a fluoroquinolone (**Option A**), is recommended to prevent SBP if the ascitic fluid protein level is less than 1.5 g/dL (15 g/L) and is associated with impaired renal function (serum creatinine ≥1.2 mg/dL [106.1 µmol/L], blood urea nitrogen ≥25 mg/dL

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[8.9 mmol/L], or serum sodium ≤130 mEq/L [130 mmol/L]) or liver failure (Child-Turcotte-Pugh score ≥9 and bilirubin level ≥3 mg/dL [51.3 µmol/L]). Fluoroquinolones are typically not used as initial treatment of SBP.

In general, large-volume paracentesis should be avoided when SBP is suspected because it may result in fluid shifts from the intervascular space to the peritoneal cavity, decreasing the effective circulating volume, activating the renin-angiotensin system, and precipitating hepatorenal syndrome. The infusion of albumin (**Option B**) following paracentesis for therapeutic purposes is recommended for higher-volume paracentesis greater than 5 L.

Trimethoprim-sulfamethoxazole (**Option D**) can be used for secondary prophylaxis of SBP but is not appropriate as initial treatment.

KEY POINTS

- Spontaneous bacterial peritonitis is diagnosed by an ascitic fluid neutrophil count of 250/µL (0.25×10^9/L) or higher.
- Treatment of spontaneous bacterial peritonitis includes a third-generation cephalosporin; albumin is infused in the presence of hepatic (bilirubin level >4 mg/dL [68.4 µmol/L]) or kidney dysfunction.

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Item 40 Answer: C

Educational Objective: Diagnose osmotic diarrhea.

The patient's stool studies are most consistent with osmotic diarrhea. Fructose malabsorption (**Option C**) is a common cause of this form of diarrhea. Chronic diarrhea can be classified as osmotic, secretory, steatorrhea, inflammatory, motility, or miscellaneous. Classification allows narrowing the differential diagnosis to guide selective laboratory testing and imaging. Stool electrolytes measured in liquid stool can help identify osmotic diarrhea, as indicated by a fecal osmotic gap, which suggests an unmeasured osmotically active intraluminal substance. The fecal osmotic gap can be calculated as follows: 290 − (2 × [stool sodium + stool potassium]). In this patient, the fecal osmotic gap is: 290 − (2 × [85 + 4.5]) = 111 mOsm/kg. An osmotic gap of greater than 100 mOsm/kg suggests an unmeasured osmotically active substance. Such substances include malabsorbed carbohydrates (e.g., lactose or fructose) and sorbitol. The latter is an artificial sweetener commonly found in sugar-free gum. Treatment of osmotic diarrhea requires avoiding offending agents, such as following a low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) and a lactose-free diet.

Intraluminal bile acid excess (**Option A**) can cause secretory diarrhea. This condition can develop after cholecystectomy or after partial ileal resection because of incomplete enterohepatic recirculation of bile acids. This form of diarrhea can be treated with a bile salt binder, such as cholestyramine. Secretory diarrhea due to bile acid excess results in an osmotic gap less than 50 mOsm/kg; given this patient's gap of 111 mOsm/kg, this cause is unlikely.

Enterotoxigenic *Escherichia coli* infection (**Option B**) is a common cause of traveler's diarrhea, characterized as watery diarrhea of a secretory subtype. The presence of an osmotic gap excludes this infection.

VIPoma (**Option D**) is a rare form of functional neuroendocrine tumor that is usually located in the pancreas. The secretion of vasoactive intestinal peptide (VIP) by this tumor results in a secretory diarrhea. This patient's stool studies are consistent with osmotic diarrhea.

KEY POINTS

- In patients with liquid stool, a calculated osmotic gap of greater than 100 mOsm/kg suggests osmotic diarrhea.
- The fecal osmotic gap is calculated as follows: 290 − (2 × [stool sodium + stool potassium]).

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Item 41 Answer: A

Educational Objective: Diagnose achalasia.

The most likely diagnosis is achalasia (**Option A**). Achalasia is associated with dysphagia with both solids and liquids, along with nonacidic regurgitation of undigested food. Additional symptoms include heartburn, weight loss, and chest pain unresponsive to acid-reducing agents. It can be idiopathic or associated with viral, autoimmune, and neurodegenerative disorders and infection (e.g., Chagas disease). The initial diagnostic test is barium esophagography or upper endoscopy, which shows dilation of the esophagus with narrowing at the gastroesophageal junction. In classic achalasia, esophageal manometry shows incomplete relaxation of the lower esophageal sphincter and aperistalsis; however, not all patients with conditions on the spectrum of achalasia-type disorders have these classic findings. Upper endoscopy reveals retained food and saliva, no signs of mechanical obstruction, and "tightness" at the gastroesophageal junction while the scope is advanced into the stomach. Treatment of achalasia aims to decrease lower esophageal sphincter pressure, which relieves symptoms. Treatments include botulinum toxin injection, pneumatic balloon dilation, peroral endoscopic myotomy, or laparoscopic myotomy. Choice of therapy depends on patient factors, type of disease, and available local expertise.

Barrett esophagus (**Option B**) is a risk factor for esophageal cancer and a complication of reflux disease, but this condition alone does not cause symptoms or dysphagia and cannot account for this patient's symptoms.

Eosinophilic esophagitis (**Option C**) may also present with dysphagia and may be initially misdiagnosed as reflux. Patients with eosinophilic esophagitis, however, usually present with solid food dysphagia rather than solid and liquid dysphagia and regurgitation symptoms. In addition, most adult patients are men, typically in their fourth decade of life, with a history of allergic disease.

Although this patient has not responded to proton pump inhibitor therapy, refractory gastroesophageal reflux disease (**Option D**) is unlikely to be the correct diagnosis given the dysphagia and weight loss. Patients with a motility disorder are often misdiagnosed with more common diseases, such as reflux. A careful history is needed to elicit regurgitation and dysphagia symptoms that suggest a motility disorder.

Viral esophagitis (**Option E**) tends to present more often with odynophagia and is more often seen in immunosuppressed individuals. Viral esophagitis does not result in regurgitation or dysphagia with both solids and liquids.

KEY POINTS

- Achalasia is associated with dysphagia with both solids and liquids, along with nonacidic regurgitation of undigested food.
- Achalasia treatment includes botulinum toxin injection, pneumatic balloon dilation, peroral endoscopic myotomy, or laparoscopic myotomy.

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Item 42 Answer: D

Educational Objective: **Treat dumping syndrome.**

The most appropriate treatment is smaller, more frequent meals (**Option D**). This patient most likely has dumping syndrome as a consequence of her sleeve gastrectomy. Dumping syndrome can follow a variety of surgical procedures, including vagotomy, pyloroplasty, Roux-en-Y bypass, sleeve gastrectomy, and esophagectomy. Early dumping syndrome, as in this patient, results from the rapid transition of food into the small intestine, causing a fluid shift and potential release of gastrointestinal hormones with vasoactive properties. Classic gastrointestinal symptoms can include abdominal pain, epigastric fullness, diarrhea, nausea, vomiting, borborygmi, and bloating. Classic vasomotor symptoms can include palpitations and tachycardia, faintness or syncope, diaphoresis, and flushing and pallor. Symptoms typically occur within 1 hour of eating. Treatment should be tiered, beginning with dietary modifications and patient education by a trained dietitian. Dietary interventions can include the pursuit of smaller and more frequent meals (at least six per day); delayed intake of fluids by at least 30 minutes after intake of solids; avoidance of rapidly absorbable carbohydrates and alcohol; increased intake of high-fiber, high-protein foods; and lying down after a meal for 30 minutes. The use of dietary supplements, such as guar gum or pectin, to increase food viscosity can also be helpful.

Pharmacologic interventions can be considered when the previously mentioned measures fail, although no pharmacologic treatment has been approved for dumping syndrome. The currently available options include acarbose (**Option A**) and, in severe cases, somatostatin analogues. Acarbose, an α-glycosidase hydrolase inhibitor that interferes with digestion of polysaccharides to monosaccharides, can be used for late symptoms of dumping syndrome if dietary intervention is only partially successful.

Metoclopramide (**Option B**) is a prokinetic approved for the treatment of gastroparesis. However, this patient does not have gastroparesis, as documented by the normal results of a gastric emptying study.

Rifaximin (**Option C**) is indicated for irritable bowel syndrome with diarrhea, which this patient does not have.

KEY POINTS

- Dumping syndrome results from rapid gastric emptying after gastric surgery; symptoms can include abdominal pain, epigastric fullness, diarrhea, nausea, vomiting, borborygmi, and bloating.
- First-line treatment of dumping syndrome is smaller, more frequent meals.

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Item 43 Answer: C

Educational Objective: **Treat hepatic adenoma in a man.**

The most appropriate management is surgical resection (**Option C**). Hepatic adenomas are benign neoplasms that often are found incidentally. They can be differentiated from focal nodular hyperplasia by abdominal MRI with gadoxetate sodium. This contrast agent is excreted in the bile ducts and therefore clarifies the presence of a hepatic adenoma, which does not typically excrete bile. Most hepatic adenomas are found in women (and are eight times more common than in men), particularly those using oral contraceptive agents. Factors posing an increased risk for malignant transformation of hepatic adenomas include adenomas greater than 5 cm in diameter and adenomas with β-catenin activation. Adenomas in men commonly have β-catenin activation; therefore, surgical resection of adenomas found in men is recommended.

Liver biopsy (**Option A**) is indicated in patients with diagnostic uncertainty but may increase the risk for bleeding; therefore, it should be performed only if the diagnosis will result in a meaningful change in management. In patients with hepatic adenomas, liver biopsy can clarify the expression of β-catenin. Because adenomas that express activated β-catenin are at increased risk for malignancy, liver biopsy is potentially useful if surgical resection is being considered. In this patient, whose risk for malignancy is already increased because he is male, liver biopsy is not necessary.

In women with hepatic adenomas that are 5 cm or smaller in diameter or that do not completely regress on cessation of oral contraceptive agents, serial abdominal imaging (**Option B**) every 6 months is recommended to evaluate for growth that would increase the risk for malignancy or hemorrhage. This option would be reasonable if this patient were female but is not appropriate for a male patient.

Benign lesions, including focal nodular hyperplasia, hepatic hemangioma, and simple hepatic cysts, do not pose appreciable risk for malignant transformation. When these lesions are diagnosed by abdominal imaging, biopsy or serial imaging thereafter is not necessary. Hepatic adenomas present a risk for hemorrhage or malignant transformation, particularly if they grow to greater than 5 cm or are found in men. Therefore, clinical observation (**Option D**) in this patient is not appropriate.

KEY POINTS

- Factors posing an increased risk for malignant transformation of hepatic adenomas include adenomas greater than 5 cm in diameter, adenomas with β-catenin activation, or adenomas found in men.
- Oral contraceptives should be discontinued in women with hepatic adenomas with follow-up CT or MRI at 6-month intervals to confirm stability or regression in the size of the lesion.

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Item 44 Answer: B

Educational Objective: Avoid overuse of proton pump inhibitor therapy.

The most appropriate management is discontinuation of omeprazole (**Option B**). This patient had upper gastrointestinal bleeding secondary to a Mallory-Weiss tear. This small mucosal defect may occur after repeated vomiting and may cause bleeding, often self-limited. In this patient, a proton pump inhibitor (PPI), omeprazole, was started during hospitalization for gastrointestinal bleeding, before endoscopy and the diagnosis of Mallory-Weiss tear, and the drug was never discontinued. PPI therapy is given to all patients suspected of having clinically significant upper gastrointestinal bleeding before endoscopy as part of their initial management and is continued following hospital discharge in patients with bleeding due to peptic ulcer disease. In patients with Mallory-Weiss tear, PPI therapy to prevent recurrent bleeding is less well studied but is not commonly used. This patient does not have a guideline-recommended indication for continued PPI use, and it would be appropriate to discontinue the omeprazole. Unnecessary continuation of PPIs after hospital discharge is a cause of PPI overuse. The goal should be to use the lowest dose to control symptoms and discontinue therapy if there is no appropriate indication. Adverse effects of PPI may include headache and gastrointestinal distress. Vitamin B_{12} deficiency, hypomagnesemia, and subsequent hypocalcemia and hypokalemia may also be associated with PPI use. Risk for community-acquired pneumonia or *Clostridioides difficile* infection also may be increased. Additional concerns have been raised regarding hip fracture, kidney injury, and dementia, but causal relationships are unproven. Because this patient has no indication for PPI use, continuing this therapy would be unnecessary.

Barium esophagography (**Option A**) is useful in the evaluation of esophageal dysphagia, especially when there is a suspicion for motility disorders or proximal lesions (e.g., Zenker diverticulum). This test would be of little yield in this patient without dysphagia whose endoscopy showed no other structural issues.

Testing for *Helicobacter pylori* (**Option C**) would be warranted for peptic ulcer disease or gastritis. Because this patient had an identified cause of his upper gastrointestinal bleeding and has no additional pathology or risk factors, *H. pylori* testing is not indicated.

In the absence of recurrent bleeding, repeat upper endoscopy (**Option D**) to assess for healing in patients with Mallory-Weiss tear is not indicated. Repeat upper endoscopy in upper gastrointestinal bleeding is reserved for select patients with peptic ulcer disease (persistent symptoms after 8 to 12 weeks of therapy, ulcers of unknown cause, or no gastric ulcer biopsy during initial endoscopy), patients with severe erosive esophagitis, and patients with esophageal varices.

KEY POINTS

- Unnecessary continuation of proton pump inhibitors (PPIs) after hospital discharge is a cause of PPI overuse.
- PPI therapy should be used at the lowest dose to control symptoms and discontinued if there is no appropriate indication.

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Item 45 Answer: A

Educational Objective: Evaluate recurrent celiac disease symptoms.

The most appropriate initial management is assessment for inadvertent gluten exposure (**Option A**). This patient with a history of celiac disease now presents with recurrent symptoms. The most common cause of recurrent celiac disease symptoms is gluten exposure. This exposure may be inadvertent. This patient's elevated tissue transglutaminase IgA level 10 years after diagnosis is suspicious for ongoing gluten exposure because serologic results typically normalize within

1 year of starting a gluten-free diet. Before nonresponsive celiac disease is diagnosed, a dietitian's evaluation of the patient's exposure to dietary gluten is important.

In patients who truly have unresponsive celiac disease, other diagnoses should be considered. Some reports suggest that approximately 10% of patients with celiac disease and recurrent symptoms have a concurrent diagnosis. Conditions to consider include HIV infection, irritable bowel syndrome, small intestinal bacterial overgrowth, microscopic colitis (**Option B**), and pancreatic insufficiency (**Option C**). This patient does not appear to have risk factors for small intestinal bacterial overgrowth or chronic pancreatitis. Microscopic colitis deserves particular attention because approximately 4% of patients with celiac disease have this condition, but it is more typically found in middle-age and older women. Because inadvertent exposure to gluten is the most common cause of recurrent celiac disease symptoms, a referral to a dietitian and exploration of possible sources of gluten exposure is the best initial management option.

Upper endoscopy with duodenal biopsy is necessary to diagnose celiac disease. This procedure also plays a role in the assessment for unresponsive celiac disease, including evaluation for intestinal lymphoma (**Option D**) or adenocarcinoma, which can complicate celiac disease and manifest as unresponsive disease. However, unresponsive celiac disease is far less likely than inadvertent gluten intake as a cause of this patient's recurrent symptoms.

KEY POINTS

- The most common cause of recurrent celiac disease symptoms is gluten exposure.
- For the assessment of recurrent symptoms of celiac disease, a dietitian should evaluate possible sources of gluten exposure.

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Item 46 Answer: A

Educational Objective: Diagnose anal fissure.

The most likely diagnosis is an anal fissure (**Option A**). Anal fissures are longitudinal mucosal tears in the anal canal characterized by anorectal pain worsened by bowel movements. Rectal bleeding with bowel movements or wiping is frequently reported. Anal fissures are idiopathic or result from trauma due to the passage of hard stool; receptive anal intercourse; or the insertion of a foreign body, such as an enema or endoscope. In this patient, the marked anorectal pain with attempted inspection of the perianal area in the context of painful defecatory bleeding is nearly diagnostic of anal fissure. A digital rectal examination is not needed in patients with severe anal pain, particularly when a thrombosed external hemorrhoid is excluded (as in this patient), because the likely diagnosis is an anal fissure. Acute anal fissures generally resolve within a few weeks with the use of sitz baths, psyllium, bulking agents, and topical vasodilators (nifedipine and nitroglycerin). Topical anesthetics and anti-inflammatory agents can be considered to address pain or bleeding, but their use is not required to promote fissure healing.

Angiodysplasia (**Option B**) can occur throughout the colon but is most common in the right colon. Angiodysplasia-related bleeding is typically painless and causes bleeding episodes that are unrelated to defecation. Because this patient has pain with defecation, angiodysplasia is not a likely cause of his symptoms.

Hemorrhoids (**Option C**) are submucosal, arteriovenous sinusoids that are part of normal anorectal anatomy and are believed to play an important role in anal canal function. Age-related changes can cause the hemorrhoid beds to slide back and forth during defecation, resulting in mucoid anal discharge, as well as perianal wetness, soiling, irritation, and/or pruritus. Hemorrhoidal bleeding is most often associated with painless defecation. The presence of pain (as in this patient) should raise suspicion for an alternative diagnosis, such as anal fissure.

Rectal cancer (**Option D**) should always be considered in a patient with new-onset rectal outlet bleeding. However, painful defecation typically does not occur with rectal cancer. In this patient, the presence of pain with defecation and the history of normal findings on screening colonoscopy 2 years previously make rectal cancer unlikely.

KEY POINTS

- Anal fissures are longitudinal mucosal tears in the anal canal characterized by anorectal pain worsened by bowel movements.
- Marked anorectal pain with attempted inspection of the perianal area in the context of painful defecatory bleeding is nearly diagnostic of anal fissure.

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Item 47 Answer: A

Educational Objective: Treat hepatitis B virus infection in the immune-active phase.

The most appropriate management is antiviral therapy (**Option A**). Treatment for hepatitis B virus (HBV) infection is advised for patients with acute liver failure, chronic infection in the immune-active phase or reactivation phase, or cirrhosis and for selected immunosuppressed patients. Chronic HBV infection is diagnosed after 6 months in patients with persistent hepatitis B surface antigen detected in serum. Chronic HBV infection is divided into phases of disease. Patients in the immune-active phase or reactivation phase have an elevated alanine aminotransferase (ALT) level, presence of hepatitis B core antibody, and an elevated HBV DNA level (>20,000 U/mL in hepatitis B e antigen [HBeAg]–positive disease or >2000 U/mL in

HBeAg-negative disease; a rise above baseline HBV DNA level in the reactivation phase). This patient has chronic HBV infection in the immune-active, HBeAg-positive phase. First-line antiviral treatment is entecavir or tenofovir for most patients. Pegylated interferon can also be used.

Treatment is necessary to decrease hepatic inflammation, the risk for progression to fibrosis, and the eventual cirrhosis that will occur without treatment. Clinical observation and surveillance (**Option B**) is not the best option for a patient with chronic HBV infection in the immune-active phase.

Patients with chronic HBV infection should receive appropriate immunizations, particularly hepatitis A virus vaccination. HBV immune globulin (**Option C**) is indicated for postexposure prophylaxis following acute exposure to HBV. It is also recommended for prevention of HBV recurrence after liver transplantation in HBsAg-positive transplant recipients. Hepatitis B immune globulin is not indicated for treatment of active HBV infection and is ineffective in the treatment of chronic active HBV infection.

A liver biopsy–confirmed diagnosis of cirrhosis can be helpful in determining the need for antiviral treatment in patients with chronic HBV infection. However, this patient with immune-active infection already has an indication for treatment. Furthermore, cirrhosis is unlikely in an asymptomatic patient without evident complications from cirrhosis and a normal hepatic ultrasound. Therefore, a liver biopsy (**Option D**) is not needed.

KEY POINTS

- Treatment of hepatitis B virus (HBV) infection is advised for patients with acute liver failure, chronic infection in the immune-active phase or reactivation phase, or cirrhosis and for selected immunosuppressed patients.
- Immune-active chronic HBV infection is defined by presence of hepatitis B core antibody, elevated alanine aminotransferase level, and HBV viral load greater than 2000 U/mL in patients negative for hepatitis B e antigen and greater than 20,000 U/mL in patients positive for hepatitis B e antigen.

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Item 48 Answer: A

Educational Objective: Treat left-sided ulcerative colitis.

The most appropriate treatment is 5-aminosalicylate (5-ASA) enemas (**Option A**). Categories of the extent of ulcerative colitis include proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction), left-sided colitis (extending from the sigmoid to the splenic flexure), and extensive colitis (beyond the splenic flexure). This patient's symptoms, colonoscopy findings, and histopathologic features are diagnostic of mild, left-sided ulcerative colitis. The initial therapy of choice would be 5-ASA enemas because they deliver active drug to the rectum and sigmoid colon. 5-ASAs are anti-inflammatory medications and the mainstay of treatment of mild to moderate ulcerative colitis, with a dose-dependent response when used to induce disease remission. Of note, combined 5-ASA therapy (oral and topical) is superior for induction of remission compared with oral or topical therapies alone. Once remission is achieved, 5-ASAs are effective in maintaining it.

5-ASA suppositories (**Option B**) deliver medication only to the rectum and therefore would be inadequate therapy for a patient with sigmoid inflammation, such as this patient.

A glucocorticoid enema (**Option C**) would be effective in inducing remission of left-sided ulcerative colitis. However, topical 5-ASA therapy is superior to topical glucocorticoids for this indication for several reasons. 5-ASAs are effective in maintenance of remission, whereas topical glucocorticoids are effective only for induction. In addition, glucocorticoids have significant adverse effects. However, guidelines recommend glucocorticoid enemas in patients with mild to moderate proctitis or left-sided colitis who are intolerant of or refractory to oral or topical 5-ASA therapy.

Oral 5-ASAs (**Option D**) are an alternative therapy if the patient declines use of 5-ASA enemas or has insufficient response. Oral 5-ASAs alone would be less optimal than topical 5-ASAs in this patient given the limited distribution of disease in the rectum and sigmoid colon.

KEY POINTS

- 5-Aminosalicylate enemas are an appropriate and effective treatment for mild, left-sided ulcerative colitis.
- 5-Aminosalicylate suppositories are an appropriate and effective treatment for mild to moderate ulcerative proctitis.

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Item 49 Answer: B

Educational Objective: Treat hypomotility disorder.

The most appropriate treatment is diet, lifestyle, and acid reduction therapy with a proton pump inhibitor (**Option B**). This patient has a hypomotility disorder. Esophageal hypomotility is associated with poor peristalsis, causing symptoms of dysphagia, and a hypotensive lower esophageal sphincter, causing symptoms of reflux. Other symptoms can include regurgitation of undigested food, in particular when the patient is in a recumbent position. Esophageal manometry shows hypotonic, weak nonperistaltic contractions in the distal esophagus. In most cases, the cause of hypotonic esophageal disease is unknown. However, secondary causes include smooth-muscle relaxants, anticholinergic agents, estrogen, progesterone, connective tissue disorders (scleroderma), and pregnancy. This patient has systemic sclerosis. Both limited and diffuse systemic sclerosis are associated with hypotonic motility disorder. Treatment includes lifestyle changes, such as eating upright and consuming a liquid or semisolid diet rather than solid food. Medical therapy includes optimization of an antireflux regimen and low-dose antidepressants for chest pain if present. Esophageal chest pain symptoms may be alleviated by low doses of tricyclic antidepressants, such as amitriptyline, or serotonin modulators, such as trazodone.

Patients with medical disorders associated with hyperperistalsis, such as diffuse (or distal) esophageal spasm and hypercontractile (nutcracker) esophagus with dysphagia may respond to smooth muscle relaxants, such as the calcium channel blocker diltiazem (**Option A**). However, smooth muscle relaxants will not help this patient with a hypotonic motility disorder and may worsen the symptoms. Treatment of this patient's hypomotility disorder can be complicated by the presence of Raynaud phenomenon, which may necessitate treatment with a calcium channel blocker.

Metoclopramide (**Option C**) is not recommended in the treatment of gastroesophageal reflux disease or esophageal motor disorders because the risk outweighs the benefits. Adverse effects of metoclopramide include tardive dyskinesia.

Laparoscopic fundoplication (**Option D**) is an antireflux surgery that creates a 360-degree wrap around the gastroesophageal junction and may benefit select patients with reflux. However, this surgery would cause an obstructive pathology in a hypotonic motility disorder and likely would worsen dysphagia symptoms.

KEY POINTS

- Esophageal hypomotility disorder is associated with poor peristalsis, causing symptoms of dysphagia, and a hypotensive lower esophageal sphincter, causing symptoms of reflux.
- Treatment of esophageal hypomotility disorder includes lifestyle changes, such as eating upright and consuming a liquid or semisolid diet rather than solid food, and acid reduction with a proton pump inhibitor.

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Item 50 Answer: C

Educational Objective: **Evaluate progressive esophageal dysphagia.**

The most appropriate diagnostic test to perform next is endoscopy with biopsy (**Option C**). This patient has esophageal dysphagia in the setting of weight loss and history of gastroesophageal reflux disease (GERD). Endoscopy should be performed to evaluate for malignancy. The most common initial presentation of esophageal carcinoma is dysphagia with solid foods; other symptoms include weight loss, anorexia, anemia caused by gastrointestinal bleeding, and chest pain. The two types of esophageal carcinoma are squamous cell carcinoma (most commonly located in the proximal esophagus) and adenocarcinoma (usually found in the distal esophagus). Risk factors for adenocarcinoma include male sex, older age, GERD, Barrett esophagus, obesity, and tobacco use. Risk factors for squamous cell carcinoma include tobacco and alcohol use, caustic injury, achalasia, past thoracic radiation, nutritional deficiencies (zinc, selenium), and poor socioeconomic status.

Barium esophagography (**Option A**) is a useful test in the evaluation of esophageal dysphagia in specific situations, such as suspicion for motility disorders or proximal lesions (e.g., Zenker diverticulum). In this case, however, the likelihood of malignancy is high given the presence of weight loss and anemia. Even if a peptic stricture secondary to GERD were suspected, biopsy would still be necessary, making endoscopy the initial test of choice.

CT of the chest (**Option B**) may be used to evaluate for extrinsic compression as a cause of dysphagia and for staging of established esophageal cancer. However, it is not a first-line test for dysphagia because it poorly visualizes the esophageal mucosa and does not provide the opportunity for biopsy.

Dysphagia occurring with solids alone suggests a mechanical obstruction, whereas dysphagia with either liquids alone or the combination of liquids and solids favors a motility disorder. An esophageal motility study (**Option D**) is an important diagnostic test in patients with nonobstructive dysphagia. In this case, however, the progression of dysphagia from solid to soft foods suggests a mechanical obstruction rather than a motility disorder, making endoscopy the preferred test.

KEY POINTS

- Dysphagia occurring with solids alone suggests a mechanical obstruction, whereas dysphagia with either liquids alone or the combination of liquids and solids favors a motility disorder.
- Dysphagia in the setting of weight loss, anemia, and history of gastroesophageal reflux disease should prompt endoscopy to evaluate for malignancy.

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Item 51 Answer: D

Educational Objective: **Diagnose hepatic sarcoidosis.**

The most appropriate diagnostic test to perform next is upper endoscopy (**Option D**). Granulomatous inflammation of the liver can result in portal hypertension, even in the absence of hepatic fibrosis. Hepatic sarcoidosis is an idiopathic condition that results in non-necrotizing granulomas. The organ most commonly affected by sarcoidosis is the lung, although the liver is also often affected. Most patients with hepatic sarcoidosis are asymptomatic; if symptoms do exist, they are typically mild and may consist of pruritus or abdominal pain due to hepatic capsule stretch. It is unclear whether immunosuppressive therapy affects the clinical course of hepatic sarcoidosis, and treatment is usually not initiated unless symptoms are severe or markers of liver inflammation are significantly abnormal. Conditions such as tuberculosis, fungal infections, brucellosis, Q fever, Hodgkin lymphoma, and drug toxicity can also cause granulomatous lesions in the liver, and steps should be undertaken to exclude these conditions before a diagnosis of sarcoidosis is accepted. The presence of skin or chest imaging findings typical of sarcoidosis also supports the diagnosis of hepatic sarcoidosis. Hepatic sarcoidosis rarely results in liver failure, but portal hypertension is common. Therefore, upper endoscopy to evaluate for esophageal varices is warranted, particularly in this patient with splenomegaly and thrombocytopenia.

This patient's abdominal ultrasound demonstrates a mildly nodular liver, which can be seen in sarcoidosis. However, because liver biopsy specimens do not demonstrate cirrhosis and ultrasound shows no masses, further imaging with CT (**Option A**) is not necessary.

Hepatobiliary iminodiacetic acid scintigraphy (**Option B**) evaluates for pathology associated with gallbladder disease or for a bile leak. In a patient without colicky pain concerning for gallbladder disease or a history of recent biliary interventions, this test would not be useful.

Magnetic resonance cholangiopancreatography (MRCP) (**Option C**) can be useful if biliary stricture is a concern. Although this patient does have an elevated alkaline phosphatase level, which can occur in the setting of biliary strictures, his ultrasound does not demonstrate dilated bile ducts. Therefore, MRCP is not indicated.

KEY POINTS

- The organ most commonly affected by sarcoidosis is the lung, although the liver is also often affected.
- In addition to sarcoidosis, conditions such as tuberculosis, fungal infections, brucellosis, Q fever, Hodgkin lymphoma and drug toxicity can also cause granulomatous lesions in the liver.

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H Item 52 Answer: D

Educational Objective: Diagnose upper gastrointestinal bleeding.

After hemodynamic resuscitation, this patient should undergo upper endoscopy (**Option D**) for evaluation of suspected upper gastrointestinal bleeding (UGIB). Peptic ulcer disease is the most common cause of UGIB (50% of patients), with most gastroduodenal ulcers caused by *Helicobacter pylori* or NSAID use. He has abdominal pain and melena in the context of ibuprofen use for osteoarthritis, which make peptic ulcer disease a likely cause of his symptoms. Hemodynamic status should be assessed in all patients, and resuscitative measures must be initiated with the goal of hemodynamic stabilization before endoscopy. Adequate intravenous access, usually with two large-bore peripheral intravenous catheters (minimum 18-gauge), should be established. Hemoglobin levels should be measured in all patients. Intravenous proton pump inhibitor therapy should be initiated before endoscopy in patients with nonvariceal UGIB. Upper endoscopy is the diagnostic test of choice to evaluate UGIB and peptic ulcer disease. Patients with UGIB should undergo upper endoscopy within 24 hours of admission following hemodynamic resuscitation; those with rapid bleeding or suspected of having variceal hemorrhage should have the procedure more emergently (within 12 hours). Endoscopy can determine the cause of bleeding and helps to risk-stratify the patient. Lesions at high risk for recurrent bleeding that require endoscopic treatment include actively bleeding peptic ulcers, ulcers with nonbleeding visible vessels, and ulcers with adherent clots.

Capsule endoscopy (**Option A**) is a first-line test to evaluate for a small-bowel source of bleeding in stable patients after normal results on upper endoscopy and colonoscopy. This patient's symptoms suggest that he has UGIB, and he has not yet undergone endoscopy or colonoscopy. Therefore, capsule endoscopy would not be appropriate.

Colonoscopy (**Option B**) is used to assess patients suspected of having lower gastrointestinal bleeding, which is typically characterized by the sudden onset of hematochezia (passage of fresh blood or clots from the colon). Colonoscopy would be indicated for this patient only if findings on upper endoscopy are normal.

If findings on upper endoscopy and colonoscopy are negative and the patient continues to experience severe gastrointestinal bleeding with hemodynamic instability, then CT angiography (**Option C**) would be appropriate. CT angiography can detect active bleeding at a rate of 0.5 to 1 mL/min and can be used to localize and direct therapy with transcatheter embolization by conventional mesenteric angiography.

KEY POINTS

- Upper endoscopy is the diagnostic test of choice to evaluate upper gastrointestinal bleeding and peptic ulcer disease.
- Patients with upper gastrointestinal bleeding should undergo upper endoscopy within 24 hours of hospital admission following hemodynamic resuscitation.

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Item 53 Answer: B H

Educational Objective: Prevent recurrence of NSAID-induced peptic ulcer disease.

The most effective ulcer preventive strategy for this patient is celecoxib and omeprazole (**Option B**). This patient has

H CONT.

experienced bleeding, a complication of NSAID-related peptic ulcer disease. Although more than 85% of cases of NSAID-related peptic ulcers heal after 6 to 8 weeks of proton pump inhibitor (PPI) therapy and avoidance of NSAIDs, reintroducing NSAIDs risks ulcer recurrence. Prevention of ulcer recurrence is therefore the most important long-term goal to reduce morbidity and mortality. If long-term NSAID use is necessary, potential treatment strategies include (1) an NSAID plus a gastroprotective agent, such as a PPI; (2) an NSAID and an H_2-blocker (**Option A**) or misoprostol; (3) a cyclooxygenase-2 (COX-2)–selective NSAID in place of a nonselective NSAID; or (4) a COX-2–selective NSAID plus a gastroprotective agent. A systematic review and meta-analysis of 82 clinical trials totaling more than 125,000 participants found the combination of a COX-2–selective NSAID plus a PPI provided the best gastrointestinal protection from ulcer recurrence and ulcer complications. Topical NSAIDs, such as diclofenac, are available by prescription for arthritis and pose a lower risk for systemic adverse effects than oral NSAIDs. They may be preferred for patients at high risk for toxicity from oral NSAIDs and/or for patients age 75 years and older. However, topical NSAIDs are often expensive. The use of a topical NSAID in this patient would be impractical considering his widespread pain. This review also showed that a COX-2–selective NSAID alone, a nonselective NSAID plus a PPI, and a nonselective NSAID plus misoprostol were more effective than a nonselective NSAID alone at reducing risk for ulcers and ulcer complications but were not as effective as a COX-2–selective NSAID and a PPI.

The use of nonselective NSAIDs with misoprostol (**Option C**) was associated with higher risk for adverse events and adverse event–related withdrawals compared with nonselective NSAIDs alone.

Switching from one nonselective NSAID (ibuprofen) to another nonselective NSAID (naproxen) (**Option D**) does not lower the risk for ulcer recurrence or ulcer complications.

KEY POINT

- The combination of a cyclooxygenase-2–selective NSAID plus a proton pump inhibitor provides the best gastrointestinal protection from ulcer recurrence and ulcer complications.

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H

Item 54 Answer: C

Educational Objective: Evaluate cause of ascites.

The most appropriate management is echocardiography (**Option C**). Ascites in a patient with liver disease is most likely to be due to cirrhosis. Portal hypertensive ascites is defined as a serum-ascites albumin gradient (SAAG) greater than or equal to 1.1 (calculated as serum albumin − ascites albumin). The differential diagnosis for high-SAAG ascites includes cirrhosis and noncirrhotic causes (e.g., heart failure). The total protein level can help differentiate cirrhotic ascites from cardiac ascites: The total protein level is low in cirrhotic ascites (<2.5 g/dL [25 g/L]) and high in cardiac ascites (≥2.5 g/dL [25 g/L]). This patient has elevated jugular venous pressure, a high SAAG, and high ascitic level of protein, suggesting a cardiac cause of ascites. Therefore, echocardiography should be performed.

The ascitic fluid cytologic finding is positive only in the setting of peritoneal carcinomatosis, and the sensitivity approaches 94% if up to three samples are submitted from three different paracenteses. In patients with peritoneal carcinomatosis, the SAAG is low and the total protein is high; therefore, ascitic fluid cytology (**Option A**) is not indicated for this patient.

The measurement of ascitic triglyceride level (**Option B**) is helpful in the diagnosis of chylous ascites. Chylous ascites may be the result of portal hypertension (high SAAG) or lymphatic obstruction (low SAAG) and high total protein level. In this patient with hemochromatosis and findings of jugular venous distention on examination, echocardiography is much more likely to establish the diagnosis than is measurement of ascitic triglyceride levels.

The American Association for the Study of Liver Disease recommends liver biopsy (**Option D**) for specific clinical situations, including diagnostic evaluation of focal or diffuse lesions on imaging studies, parenchymal liver diseases, chronically elevated liver test results of unknown cause, fever of unknown origin, and therapeutic planning and staging of parenchymal liver diseases. Liver biopsy is of little use in a patient with known cirrhosis and clinical evidence of portal hypertension.

KEY POINTS

- The differential diagnosis for ascitic fluid with a high serum-ascites albumin gradient includes cirrhosis and noncirrhotic causes (e.g., heart failure).
- The total protein level is low in cirrhotic ascites (<2.5 g/dL [25 g/L]) and high in cardiac ascites (≥2.5 g/dL [25 g/L]).

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Item 55 Answer: B

H

Educational Objective: Diagnose drug-induced liver injury.

The most likely diagnosis is drug-induced liver injury (**Option B**). Elevations in alkaline phosphatase and serum total bilirubin levels and proportionally lesser elevations of aminotransferase levels indicate cholestatic hepatitis, the most common cause of which is drug-induced cholestasis. Drug-induced liver injury can result from exposure to prescription and nonprescription drugs as well as herbal and dietary supplements, even if the exposure occurred 6 months before symptom onset. The likely source of this patient's cholestasis is the amoxicillin-clavulanate she received for diverticulitis. Antibiotics (particularly amoxicillin-clavulanate) and antiepileptic medications (phenytoin and valproate) are among the most common medications associated with drug-induced liver injury, representing 60% of cases. Liver injury typically resolves after discontinuation of the offending drug; resolution of liver injury supports the diagnosis. Jaundice that occurs with cholestatic drug reactions can take months to resolve. Treatment of drug-induced liver disease is largely supportive, with removal of the offending agent. Liver transplantation can be considered in patients who have evidence of liver failure (i.e., those for whom liver injury is associated with encephalopathy and coagulopathy).

Autoimmune hepatitis (**Option A**) presents predominantly as a hepatocellular injury. The presentation of autoimmune hepatitis can vary from asymptomatic elevation of aminotransferase levels to extrahepatic symptoms, such as myalgia and malaise, to acute liver failure. This patient's cholestatic liver injury pattern is not consistent with autoimmune hepatitis.

Hepatitis A virus (**Option C**) is transmitted by the fecal-oral route. International travel is a risk factor. A prodrome of malaise, nausea, vomiting, fever, and right-upper-quadrant discomfort is followed by development of jaundice and a hepatocellular pattern of injury. Despite this patient's international travel, her illness is not compatible with hepatitis A virus infection because the incubation period for this infection is 15 to 50 days.

Primary biliary cholangitis (**Option D**) is an unlikely cause of subacute cholestatic liver injury in this 73-year-old patient. Most patients are diagnosed between the fourth and fifth decades of life and either present with pruritus or have incidentally discovered elevated alkaline phosphatase level.

KEY POINTS

- Drug-induced liver disease can result from exposure to prescription and nonprescription drugs as well as herbal and dietary supplements, even if the exposure occurred 6 months before symptom onset.
- The most common cause of cholestatic hepatitis is drug-induced liver injury.

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Item 56 Answer: C

Educational Objective: **Diagnose oropharyngeal dysphagia.**

The most likely diagnosis is oropharyngeal dysphagia (**Option C**), also called transfer dysphagia. Swallowing has three phases: oral phase (food bolus forms and transfers to the back of the throat), pharyngeal phase (bolus is safely positioned in the upper throat, the soft palate elevates, the epiglottis protects the trachea, the tongue moves backward, and the pharyngeal wall moves forward), and esophageal phase (bolus enters the esophagus with relaxation of the upper esophageal sphincter). When the first two phases fail to position a bolus in the throat for entry into the esophagus, choking, coughing, and nasal regurgitation of solids and liquids may occur. These symptoms pose a risk for aspiration pneumonia. Other presenting symptoms may include hoarseness (resulting from laryngeal nerve damage) and dysarthria (from weakness of the soft palate or pharyngeal constrictors), both suggesting an underlying neurologic disorder. Indeed, oropharyngeal dysphagia may be an early symptom or presenting sign of neurologic disorders, such as Parkinson disease and stroke. It is important to recognize oropharyngeal dysphagia by history because the initial recommended study is a modified barium swallow (with a range of liquid and solid consistencies) and videofluoroscopy. Endoscopy and esophageal manometry have a limited role in the evaluation of oropharyngeal dysphagia. Management consists of dietary changes and a swallowing exercise program.

Patients with achalasia (**Option A**) often have dysphagia with solids and liquids, along with nonacidic oral regurgitation of undigested food. Choking and aspiration are often late-stage symptoms that may occur after long-standing regurgitation and other dysphagia symptoms. This patient does not have any regurgitation and can swallow soft foods, making achalasia an unlikely diagnosis.

Incarcerated paraesophageal hernia (**Option B**) is often associated with pain and typically presents with solid dysphagia before liquid dysphagia. This patient has no chest pain and is experiencing liquid dysphagia; thus, incarcerated paraesophageal hernia is an unlikely diagnosis.

This patient is unlikely to have a mechanical obstruction, such as a peptic stricture (**Option D**), because he has more trouble swallowing liquids than solids. In addition, a peptic stricture is often more chronic, with gradual worsening.

KEY POINTS

- Common symptoms of oropharyngeal dysphagia include choking, coughing, and nasal regurgitation of solids and liquids.
- The initial evaluation of oropharyngeal dysphagia is a modified barium swallow (with a range of liquid and solid consistencies) and videofluoroscopy.

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Item 57 Answer: D

Educational Objective: **Treat hepatic failure with liver transplantation.**

The most appropriate management is referral for liver transplantation (**Option D**). Referral for liver transplantation is indicated in patients whose MELD-Na (Model for End-Stage

Liver Disease–sodium) score is 15 or greater and in those with findings of decompensated disease, such as ascites, jaundice, hepatocellular carcinoma, hepatorenal syndrome, variceal hemorrhage, spontaneous bacterial peritonitis, and hepatic encephalopathy. Although the MELD-Na score is used to prioritize patients on the liver transplant list, patients with symptoms of hepatic decompensation should be referred to a liver transplant center for consideration of transplantation. Symptoms of liver decompensation herald a high risk for clinical worsening and a 2-year mortality rate of 50%. The average 1- and 5-year survival rates after liver transplantation are 92% and 75% to 85%, respectively. Therefore, this patient with advancing symptoms of liver decompensation should be considered for liver transplantation, regardless of the MELD-Na score.

Patients with active hepatitis C virus infection can be considered for antiviral therapy, although the use of protease inhibitors (**Option A**) in patients with decompensated cirrhosis has been associated with worsening liver failure. These medications should not be used in patients with advancing symptoms of liver dysfunction. Patients with decompensated cirrhosis should see a hepatologist before treatment and be considered for liver transplantation.

The development of hepatic encephalopathy should prompt an evaluation for potential reversible causes. Infections, gastrointestinal bleeding, volume depletion, and medications with sedating properties are common precipitants of hepatic encephalopathy and, if present, should be treated promptly. The initiation of lactulose therapy is appropriate in this setting, but the initiation of rifaximin (**Option B**) may be limited by cost. Rifaximin does not necessarily need to be added at this time unless lactulose alone does not adequately control symptoms.

Dietary protein intake was previously thought to be a potential precipitant for hepatic encephalopathy, but this idea has been refuted. Even patients with hepatic encephalopathy should not be given a protein-restricted diet (**Option C**).

KEY POINTS

- Findings of hepatic decompensation include ascites, jaundice, hepatocellular carcinoma, hepatorenal syndrome, variceal hemorrhage, spontaneous bacterial peritonitis, and hepatic encephalopathy.
- Patients with findings of hepatic decompensation should be referred for consideration of liver transplantation.

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Item 58 Answer: D

Educational Objective: Manage hepatitis C virus infection in a patient with short life expectancy.

The most appropriate management is no further hepatitis C virus (HCV)–related testing or treatment (**Option D**). The 2018 guidelines suggest that all adults should be screened for HCV with an HCV antibody test. In patients positive for HCV antibody, a positive HCV RNA result indicates active infection. Acute hepatitis C virus infection refers to the first 6 months after initial infection. Because there is a 20% to 50% chance that infection will spontaneously resolve during this period, monitoring HCV RNA for at least 12 to 16 weeks before starting treatment is often recommended. All patients with chronic HCV infection should be treated regardless of fibrosis stage, except those who have a short life expectancy, such as this patient with metastatic pancreatic cancer. Because this patient will not benefit from treatment, it is most appropriate to provide no further testing or treatment.

Patients may request specific diagnostic or therapeutic interventions that may be inappropriate. Examples include requests for antibiotic therapy for a suspected viral infection (**Option A**) and aggressive chemotherapy in a debilitated patient with cancer. Although the physician needs to respect patient autonomy, this duty must be weighed against the potential harms of inappropriate interventions, possible secondary effects (e.g., antimicrobial resistance caused by inappropriate antibiotic prescribing), and responsible stewardship of medical resources. When there is no evidence that the desired diagnostic or therapeutic intervention will provide clinical benefit, physicians are not obligated to provide the service. Because this patient has a limited life expectancy, she should not be offered treatment for HCV.

The first step in the diagnosis of chronic HCV infection is HCV antibody testing and, if the result is positive, HCV RNA quantification. Patients with positive HCV antibody and RNA test results have active infection, and a genotype test should be performed to guide selection of antiviral therapy. Because this patient will not benefit from treatment, additional testing (**Option B**) is not indicated.

All patients infected with HCV should be tested for hepatitis B virus (HBV) and HIV infections (**Option C**) because of the potential shared routes of transmission. HBV reactivation can be seen during treatment of HCV infection with direct-acting antiviral therapy. This testing is not necessary in this patient with a limited life expectancy.

KEY POINTS

- All patients with chronic hepatitis C virus infection should be offered treatment regardless of fibrosis stage, except those who have a short life expectancy.
- When there is no evidence that the patient's requested diagnostic or therapeutic intervention will provide clinical benefit, physicians are not obligated to provide the service.

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Item 59 Answer: B

Educational Objective: Diagnose medication-related diarrhea.

The most appropriate management is discontinuation of ibuprofen (**Option B**). The evaluation of chronic diarrhea starts with a history and physical examination, followed by selective diagnostic testing that includes laboratory analyses and imaging, depending on the differential diagnosis. Many drugs can cause diarrhea, and it can be difficult to identify a drug-related cause of diarrhea in patients taking multiple medications. The temporal relationship between starting a drug and diarrhea onset can be helpful when present but is not always obvious. A reasonable strategy is to discontinue a potential culprit drug, if possible, and assess the effect on the patient's symptoms. This patient's history is notable for regular use of ibuprofen, an NSAID implicated in chronic diarrhea. The mechanism by which ibuprofen causes diarrhea is uncertain, but this effect sometimes occurs in the context of microscopic colitis. Discontinuing ibuprofen may lead to resolution of his symptoms, obviating the need for further evaluation.

Colonoscopy (**Option A**) is used selectively in the diagnostic evaluation of chronic diarrhea and is indicated for patients who have rectal bleeding, are age 50 years or older, have alarm symptoms (e.g., weight loss), or have suspected Crohn disease or ulcerative colitis. This patient's lack of alarm symptoms and normal fecal calprotectin level make Crohn disease and ulcerative colitis less likely. His diarrhea may be due to NSAID-induced microscopic colitis, which can be diagnosed via colonoscopy with biopsies; however, this diagnosis can be determined by discontinuing ibuprofen and monitoring his symptoms.

Tissue transglutaminase IgA levels are elevated in celiac disease, which is another cause of chronic diarrhea. Although measuring this antibody (**Option C**) is generally indicated in patients with chronic diarrhea, its diagnostic utility is reduced in the setting of a gluten-free diet. If the symptoms do not improve with withdrawal of ibuprofen, the patient can discontinue the gluten-free diet and, after an appropriate interval, be tested for celiac disease.

Video capsule endoscopy (**Option D**) allows visualization of the small intestine. Capsule endoscopy can be of value for diagnosing Crohn disease isolated to the small intestine; this cause of chronic diarrhea is less likely in this patient given his normal fecal calprotectin level. NSAID-induced enteropathy, characterized by inflammation and ulcers in the small intestine, can also be diagnosed via video capsule endoscopy, but discontinuing ibuprofen may lead to symptom resolution without the need for this procedure.

KEY POINT

- Many drugs can cause chronic diarrhea; discontinuing a potential culprit drug may relieve symptoms and obviate the need for further diagnostic testing.

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Item 60 Answer: D

Educational Objective: Diagnose small-bowel bleeding.

The most appropriate diagnostic test to perform next is video capsule endoscopy (**Option D**). The type of lesion responsible for small bowel bleeding depends on patient age but not sex or ethnicity. Patients younger than 40 years are likely to have small-bowel bleeding due to inflammatory bowel disease, Dieulafoy lesions, neoplasia, Meckel diverticulum, or a polyposis syndrome. Patients older than 40 years are likely to have bleeding due to angiodysplasia, Dieulafoy lesions, neoplasia, or NSAID-related ulcers. If a bleeding source is not identified on initial endoscopy and colonoscopy, second-look upper endoscopy or colonoscopy should be performed if the initial studies were of low quality. Push enteroscopy may be pursued in lieu of endoscopy to visualize the distal duodenum and proximal jejunum. Repeat colonoscopy should include intubation of the terminal ileum. This patient is suspected of having small-bowel bleeding as the source of his iron deficiency anemia, given the lack of a source on high-quality upper endoscopy and colonoscopy. This bleeding can be further characterized as occult given the absence of overt signs of gastrointestinal bleeding, including melena and hematochezia. Video capsule endoscopy noninvasively evaluates the entire small bowel. This test uses a nondigestible wireless capsule camera that is swallowed or placed endoscopically. Capsule endoscopy allows noninvasive evaluation of the entire small bowel in 79% to 90% of patients, with a diagnostic yield of 38% to 83% in patients suspected of having small-bowel bleeding. The American College of Gastroenterology has recommended it as a first-line procedure for further evaluation of the small bowel after upper and lower gastrointestinal sources of occult gastrointestinal bleeding have been excluded. Alternatively, in uncomplicated asymptomatic patients with iron deficiency anemia and negative bidirectional endoscopy, a trial of initial iron supplementation over the routine use of video capsule endoscopy is conditionally suggested by the American Gastroenterological Association.

CT angiography (**Option A**) and tagged red cell scintigraphy (technetium-99m-labeled red cell scintigraphy) (**Option C**) require active bleeding to be effective in identifying a source for small-bowel bleeding (bleeding rates of 0.3 mL/min for CT angiography and 0.1-0.2 mL/min for tagged red cell scintigraphy). This patient has no signs of active bleeding; therefore, neither CT angiography nor a tagged red cell scintigraphy would be effective in identifying a bleeding source in the small bowel.

Barium examinations of the small bowel (**Option B**) have demonstrated a low yield (only 3% to 17%) in identifying a source of suspected small-bowel bleeding and are no longer recommended for this purpose.

KEY POINT

- For evaluating stable patients suspected of having small-bowel bleeding, video capsule endoscopy is the preferred test after nondiagnostic upper endoscopy and colonoscopy.

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Item 61 Answer: B

Educational Objective: Treat moderate to severe relapsed ulcerative colitis.

The most appropriate treatment is combination therapy with azathioprine and infliximab (**Option B**). This patient has recurrent symptoms of ulcerative colitis on tapering of glucocorticoids. Although glucocorticoids induce remission in moderate to severe flares of ulcerative colitis, they should not be used to maintain remission. Azathioprine and the anti-tumor necrosis factor (anti-TNF) agents infliximab and golimumab induce and maintain remission in moderate to severe ulcerative colitis. Combination therapy with infliximab and azathioprine is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing. Before initiation of anti-TNF agents, patients should undergo testing for latent tuberculosis because of an increased risk for reactivation of tuberculosis during therapy. If latent tuberculosis is present, treatment with isoniazid should be administered for at least 2 months before initiation of anti-TNF therapy. Patients should also be assessed for chronic hepatitis B virus infection before starting anti-TNF therapy and receive treatment if needed.

Thiopurines (azathioprine and mercaptopurine) are immunomodulators used as glucocorticoid-sparing agents in ulcerative colitis. They have a slow onset of action (2-3 months), and patients require a tapering glucocorticoid regimen to bridge the interval until the thiopurines take effect. Thiopurines are no more effective than placebo in inducing short-term symptomatic remission and should not be used in this manner. Given the slow onset of action, beginning azathioprine alone (**Option A**) is inappropriate.

Certolizumab (**Option C**), an anti-TNF agent, treats moderate to severe Crohn disease resistant to glucocorticoids or immunomodulators. This agent has no role in treatment of ulcerative colitis.

Multimatrix budesonide (**Option D**) is a colonic delivery system of budesonide that allows directed therapy throughout the colon with fewer glucocorticoid systemic adverse effects. It is effective in inducing remission in mild to moderate ulcerative colitis unresponsive to 5-aminosalicylate. However, because multimatrix budesonide is effective only in inducing remission, it would be inappropriate for this patient, who requires an induction and a maintenance agent. In addition, he is already receiving a glucocorticoid and is steroid dependent.

KEY POINTS

- Combination therapy with infliximab and azathioprine is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing in ulcerative colitis.

(Continued)

KEY POINTS *(continued)*

- Before initiation of anti-tumor necrosis factor agents, patients should undergo testing for latent tuberculosis and hepatitis B virus infection.

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Item 62 Answer: A

Educational Objective: Identify the proper surveillance interval following removal of a large tubular adenoma.

The appropriate surveillance interval for a patient with an 11-mm tubular adenoma polyp is 3 years (**Option A**). A 3-year colonoscopy interval is appropriate for patients with larger adenomas (≥10 mm), 5 to 10 tubular adenomas less than 10 mm, adenomas with tubulovillous or villous histology, or adenomas with high-grade dysplasia. A 3- to 5-year interval is appropriate for three or four tubular adenomas less than 10 mm. Between 20% and 53% of adults older than age 50 years have premalignant adenomas of the colon detected on screening, and 3% to 8% of the adenomas have advanced histologic features. Because adenomas are an intermediary step in the progression from normal colonic mucosa to colon cancer, identification and management of polyps are critical. The progression of adenoma to carcinoma takes approximately 8 to 10 years. Adenomas with any degree of villous histology or high-grade dysplasia have greater malignant potential. Risk is also substantially increased in polyps 10 mm or larger.

A 7- to 10-year colonoscopy interval (**Option B**) is appropriate for patients with one or two small (<10 mm) tubular adenomas. This interval is not recommended for this patient with an 11-mm tubular adenoma. For patients with more than 10 adenomas found on a single examination, a genetic cause of disease should be investigated and colonoscopy should be repeated in 1 year.

Fecal-based testing with DNA (**Option C**) and fecal occult blood testing (**Option D**) are options for cancer screening recommended for asymptomatic persons at average risk for colorectal cancer. These screening strategies are not recommended for surveillance in patients at increased risk for colorectal cancer or in whom polyps have been identified on colonoscopy.

KEY POINTS

- A 3-year colonoscopy interval is appropriate for patients with larger adenomas (≥10 mm), 5 to 10 tubular adenomas less than 10 mm, adenomas with tubulovillous or villous histology, or adenomas with high-grade dysplasia; a 3- to 5-year interval is appropriate for three or four tubular adenomas less than 10 mm.
- A 7- to 10-year colonoscopy interval is appropriate for patients with one or two small (<10 mm) tubular adenomas.

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Item 63 Answer: B

Educational Objective: **Diagnose chronic mesenteric ischemia.**

The most appropriate diagnostic test to perform next is CT mesenteric angiography (**Option B**). Chronic mesenteric ischemia (CMI) is an uncommon condition most often resulting from atherosclerotic narrowing of the mesenteric arteries. The classic symptom triad of CMI is postprandial abdominal pain, sitophobia (fear of eating), and weight loss, but this set of symptoms is seen in only 30% of patients with CMI. In the setting of recurrent postprandial abdominal pain, CMI should be suspected. Pain begins approximately 30 minutes after food ingestion as the fixed narrowing of the mesenteric arteries prevents blood flow from increasing and meeting the increased functional demand of the small bowel, with resultant ischemia. The diagnosis of CMI requires exclusion of alternative causes of postprandial abdominal pain and weight loss, along with compatible imaging findings. CT or magnetic resonance angiography findings suggesting CMI include severe stenosis (>70%) of two of the three mesenteric arteries. If the patient has compatible symptoms and suggestive angiographic findings, and alternative explanations for postprandial abdominal pain have been excluded, then the diagnosis of CMI is secure. In patients with symptoms suggestive of CMI, CT mesenteric angiography is the recommended initial diagnostic imaging test because it allows for rapid and accurate assessment of the mesenteric vasculature. Duplex ultrasonography of the mesenteric vessels is a reasonable screening modality to detect high-grade stenosis of the celiac and superior mesenteric arteries for patients being evaluated in an outpatient setting.

Capsule endoscopy (**Option A**) can visualize the small intestine and is often used in the evaluation of small-bowel bleeding. However, this patient's symptoms suggest ischemic pain rather than bleeding, so capsule endoscopy will provide no diagnostic value.

A gastric emptying study (**Option C**) helps assess for gastroparesis as a cause of postprandial symptoms. Gastroparesis entails delayed gastric emptying without mechanical obstruction and with the cardinal symptoms of nausea, vomiting, early satiety, aand postprandial upper abdominal pain. For this patient, however, the presence of atherosclerotic vascular disease, an abdominal bruit and absent nausea, early satiety, and risk factors for gastroparesis support CT mesenteric angiography as the next diagnostic step.

Ultrasonography of the gallbladder (**Option D**) would be appropriate if biliary colic were suspected. Abdominal pain from biliary colic is episodic, severe, and steady and is often located in the epigastrium or right upper quadrant, as in this patient. However, biliary pain recurs at different intervals, whereas this patient's pain occurs daily. Therefore, ultrasonography would not be appropriate for this patient.

KEY POINTS

- The diagnosis of chronic mesenteric ischemia requires exclusion of alternative causes of postprandial abdominal pain and weight loss, along with compatible imaging findings.
- CT or magnetic resonance angiography findings suggesting chronic mesenteric ischemia include severe stenosis (>70%) of two of the three mesenteric arteries.

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Item 64 Answer: A

Educational Objective: **Manage dual aspirin and anticoagulant therapy during lower gastrointestinal bleeding.**

The most appropriate management of antiplatelet and anticoagulant therapy in this patient is to hold apixaban (**Option A**). This patient most likely developed postpolypectomy bleeding that was exacerbated by aspirin and apixaban use. Because he has hemodynamically significant lower gastrointestinal bleeding, the initial steps are intravascular resuscitation and withholding apixaban. The duration of the anticoagulant effect of the direct oral anticoagulants (DOACs), including apixaban, is limited because of their relatively short half-life. In most cases of lower gastrointestinal bleeding, simply holding the DOAC is sufficient.

Andexanet is a recombinant modified factor Xa protein used to reverse the anticoagulant effects of apixaban and rivaroxaban in patients with life-threatening or uncontrolled bleeding. Its use has been associated with serious and life-threatening events, including myocardial infarction, stroke, cardiac arrest, and sudden death. For life-threatening bleeding related to Xa inhibitors, such as apixaban, the American Society of Hematology suggests stopping the oral direct Xa inhibitor and considering treatment with four-factor prothrombin complex concentrates or andexanet alfa (**Options B, D**). Because of the lack of comparative data, a preferred strategy cannot be identified. This patient does not have life-threatening uncontrolled bleeding (as indicated by the response to intravenous resuscitation) and therefore does not need apixaban reversal therapy.

For secondary prevention of cardiovascular disease, the risk of interrupting aspirin therapy (**Option C**) is substantial. Studies have shown that discontinuation of long-term low-dose aspirin therapy for secondary prevention is associated with a threefold increased risk for cardiovascular or cerebrovascular events, with 70% of such events occurring within 7 to 10 days of discontinuation. The American College of Gastroenterology and the British Society of Gastroenterology have recommended that to avoid thromboembolic events,

CONT.

aspirin for secondary prophylaxis in patients with established cardiovascular disease should not be discontinued in patients with lower gastrointestinal bleeding. If aspirin is discontinued, it should be restarted as soon as possible following hemostasis.

KEY POINT

- The duration of the anticoagulant effect of the direct oral anticoagulants (DOACs) is limited because of their short half-life; in most cases of gastrointestinal bleeding, simply holding the DOAC is sufficient.

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Item 65 Answer: A

Educational Objective: Evaluate lower gastrointestinal bleeding in a hemodynamically stable patient.

The most appropriate next diagnostic test is colonoscopy (**Option A**). This patient likely has lower gastrointestinal bleeding. She has no signs of active bleeding and is hemodynamically stable. Given her age, comorbid conditions, and significant decrease in hemoglobin, observation and urgent colonoscopy are warranted. Colonoscopy should be performed within 24 hours of presentation after adequate colon preparation, which may include rapid preparation. Colonoscopy identifies a source of lower gastrointestinal bleeding in two thirds of patients.

There is no need for CT angiography (CTA) (**Option B**) or tagged red cell scintigraphy (technetium-99m–labeled red cell scintigraphy) (**Option C**) to detect and localize a site for active bleeding. CTA is the initial diagnostic test in patients who are hemodynamically unstable or have rapid ongoing bleeding, followed by immediate upper endoscopy if CTA does not reveal a source of bleeding. Because this patient is hemodynamically stable and does not have active bleeding, CTA would not be appropriate. Although tagged red cell scintigraphy can detect bleeding rates as low as 0.1 mL/min, its usefulness in acute lower gastrointestinal bleeding is debated. Sensitivity of nuclear studies for the detection of a lower gastrointestinal bleeding site varies from 60% to 93%. Although nuclear studies may be able to detect lower gastrointestinal bleeding, precise anatomic location is inferior to that provided by first-line diagnostic tests. Tagged red cell scintigraphy may be considered when results of first-line tests, such as CTA, angiography, or colonoscopy, are negative.

Although this patient takes aspirin, her presentation of multiple maroon stools does not suggest upper gastrointestinal bleeding. Furthermore, she is receiving long-term gastric protective therapy with omeprazole, further reducing the risk for upper gastrointestinal bleeding. If colonoscopy results fail to reveal a cause of bleeding, upper endoscopy (**Option D**) can be considered as a secondary test. This patient's aspirin therapy is prescribed for secondary prevention of atherosclerotic cardiovascular disease and should be continued uninterrupted. If discontinuation of aspirin is necessary in these cases, it should be reinstated as soon as possible following hemostasis.

KEY POINTS

- In hemodynamically stable patients without evidence of rapid lower gastrointestinal bleeding, colonoscopy is the first test of choice.
- Although nuclear studies may be able to detect lower gastrointestinal bleeding, precise anatomic location is inferior to that provided by first-line diagnostic tests, such as colonoscopy, CT angiography, and conventional angiography.

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Item 66 Answer: B

Educational Objective: Treat moderate to severe Crohn disease.

The most appropriate treatment is starting infliximab (**Option B**), an anti–tumor necrosis factor (anti-TNF) agent. The patient presented with a flare of severe ileocolonic Crohn disease. She has required several courses of glucocorticoid treatment because maintenance therapy with azathioprine, an immunomodulator, failed. The anti-TNF agents infliximab, adalimumab, and certolizumab treat moderate to severe Crohn disease that is resistant to glucocorticoids or immunomodulators. Combination therapy with infliximab and azathioprine is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing. Before initiation of anti-TNF agents, patients should undergo testing for latent tuberculosis because of an increased risk for reactivation of tuberculosis during therapy. If latent tuberculosis is present, treatment with isoniazid should be administered for at least 2 months before initiation of anti-TNF therapy. Patients should also be assessed for chronic hepatitis B virus infection before starting anti-TNF therapy and receive treatment if needed.

Various formulations of oral and intravenous glucocorticoids are commonly used to treat mild to severe flares of Crohn disease. Although they are effective in inducing remission, they are not effective for maintenance therapy and have significant adverse effects. Controlled-release oral budesonide (**Option A**) is a glucocorticoid that is effective in inducing remission in mild to moderate ileocolonic Crohn disease. This patient has severe ileocolonic disease, however, which will likely lead to failure of induction with oral budesonide.

Thiopurines (azathioprine and 6-mercaptopurine) are immunomodulators used as glucocorticoid-sparing agents in Crohn disease. They have a slow onset of action

(2-3 months), and patients require a tapering glucocorticoid regimen to bridge the interval until the thiopurine takes effect. Azathioprine and 6-mercaptopurine are equivalent immunomodulators, and changing from one to the other (**Option C**) would have no benefit in this patient.

Although several formulations of 5-aminosalicylates deliver the drug to the small bowel, they are not efficacious in small-bowel Crohn disease. Sulfasalazine (**Option D**) is effective for treating symptoms of colonic Crohn disease that is mild to moderately active and can be used as treatment for this patient population. Given its lack of efficacy in small-bowel Crohn disease and this patient's severe colonic disease, initiating sulfasalazine would not be appropriate.

KEY POINTS

- An anti-tumor necrosis factor agent is most likely to induce and maintain remission of moderate to severe ileocolonic Crohn disease resistant to glucocorticoids or immunomodulators.
- Combination therapy with an anti-tumor necrosis factor and an immunomodulator is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing in moderate to severe Crohn disease.

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Item 67 Answer: B

Educational Objective: Diagnose small intestinal bacterial overgrowth.

The appropriate management is a glucose breath test (**Option B**). The patient's 5-month history of diarrhea, characterized as bowel movements containing oil droplets and necessitating multiple flushes, is consistent with steatorrhea. Causes of fat malabsorption include pancreatic dysfunction, infections (e.g., giardiasis and Whipple disease), celiac disease, tropical sprue, and small intestinal bacterial overgrowth (SIBO). SIBO is caused by various conditions, including impaired motility, strictures (e.g., in Crohn disease), or blind loops (e.g., small-bowel diverticula). The patient's jejunal diverticulum is a blind loop and a key risk factor for SIBO. The pathogenesis of steatorrhea in SIBO is thought to be due to the deconjugation of bile salts by excessive intraluminal bacteria, interfering with formation of micelles that are necessary for fat absorption. SIBO can be diagnosed in the appropriate clinical context with both typical symptoms (abdominal discomfort, flatulence, bloating, and diarrhea) and a confirmatory test, such as a glucose breath test, in which exhaled hydrogen and methane (byproducts of bacterial metabolism of ingested glucose) are measured after glucose administration. Glucose breath tests are approximately 80% sensitive but only 40% specific for diagnosing SIBO. Empiric antibiotic therapy with monitoring for improvement in symptoms may be reasonable in patients with a high probability of SIBO.

Eluxadoline (**Option A**), a mixed κ- and μ-opioid receptor agonist and δ-opioid receptor antagonist, decreases the frequency of bowel contractions and treats diarrhea-predominant irritable bowel syndrome. This patient's age at symptom onset and lack of abdominal pain, as well as the presence of a risk factor for SIBO, make irritable bowel syndrome a less likely diagnosis.

Stool should be tested for *Clostridioides difficile* toxin (**Option C**) in patients with suspected *C. difficile* colitis, usually in the setting of antecedent antibiotic use. This patient's steatorrhea in the absence of risk factors for *C. difficile* infection makes this diagnosis unlikely.

Upper endoscopy with duodenal biopsy (**Option D**) is indicated in the setting of chronic diarrhea when serologic results suggest celiac disease. In this patient, the normal tissue transglutaminase IgA level makes celiac disease unlikely.

KEY POINTS

- Causes of fat malabsorption include pancreatic dysfunction, infections (e.g., giardiasis and Whipple disease), celiac disease, tropical sprue, and small intestinal bacterial overgrowth.
- Small intestinal bacterial overgrowth can be diagnosed in the appropriate clinical context with both typical symptoms (abdominal discomfort, flatulence, bloating, and diarrhea) and a positive result on a glucose breath test.

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Item 68 Answer: B

H

Educational Objective: Manage low-risk upper gastrointestinal bleeding.

The most appropriate management for this patient with upper gastrointestinal bleeding due to a low-risk duodenal ulcer is a once-daily oral proton pump inhibitor (PPI), initiation of oral intake of food, and early planning for hospital discharge (**Option B**). In patients with bleeding peptic ulcer disease, factors that increase the risk for recurrent bleeding and death include tachycardia, hypotension, age older than 60 years, hemoglobin level less than 7 g/dL (70 g/L) (8 g/dL [80 g/L] in patients with cardiovascular disease), and comorbid illness. This young patient is otherwise healthy, has a hemoglobin level above 7 g/dL (70 g/L), and is hemodynamically stable. Upper endoscopy for risk stratification revealed a clean-based ulcer, which is a predictor of low risk for recurrent hemorrhage. The other lesion at low risk for rebleeding includes an ulcer with a pigmented spot. These low-risk lesions do not require endoscopic therapy. Patients with peptic ulcer disease and low-risk stigmata can start oral feeding within 24 hours

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of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital. NSAIDs should be discontinued in patients with NSAID-induced bleeding peptic ulcer disease. If there is no effective alternative to NSAIDs, a selective cyclooxygenase-2 inhibitor plus a once-daily PPI should be used.

Intravenous PPI therapy and hospital observation for 72 hours (**Option A**) would be appropriate for patients with high-risk lesions. Lesions at high risk for recurrent bleeding that require endoscopic treatment include actively bleeding peptic ulcers, ulcers with nonbleeding visible vessels, and ulcers with adherent clots. An adherent clot should be irrigated with the intention of removing the clot; if clot removal is successful, the underlying stigmata is addressed. In this patient, intravenous PPI therapy plus hospital observation for 72 hours is not an appropriate management strategy given the low risk for rebleeding from a clean-based ulcer.

Once-daily oral PPI, no feeding, and hospital observation for 72 hours (**Option C**) is insufficient therapy for high-risk lesions and is unnecessary in patients with low-risk lesions.

If bleeding recurs, endoscopic therapy should be repeated, but routine second-look endoscopy (**Option D**) is not recommended.

KEY POINTS

- NSAIDs should be discontinued in patients with NSAID-induced bleeding peptic ulcer disease; if treatment must be continued, a selective cyclooxygenase-2 inhibitor plus a once-daily proton pump inhibitor should be used.
- Patients with peptic ulcer disease and low risk for rebleeding (clean-based ulcer, ulcers with pigmented spots) can start oral feeding within 24 hours of endoscopy, receive once-daily oral proton pump inhibitor therapy, and be discharged from the hospital.

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Item 69 Answer: D

Educational Objective: Manage a serous cystadenoma.

The most appropriate management for the patient's serous cystadenoma is no further evaluation or intervention (**Option D**). Characteristic findings of serous cystadenomas include multicystic, lobulated structures (sometimes described as a "bunch of grapes"), which may have a central fibrosis scar or calcification. Pancreatic cysts are being detected more frequently because of increased use of imaging and improved imaging techniques; these cysts may be found in 15% of individuals undergoing abdominal imaging. Cystic neoplasms of the pancreas are subcategorized as mucin-producing and non-mucin-producing cysts. Mucin-producing cysts, including intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, are thought to have malignant potential, but many never become malignant. Non-mucin-producing cysts, such as a serous cystadenoma, have no malignant potential and can often be identified by their characteristic imaging features. These cysts require no further evaluation unless symptomatic.

For patients in whom the diagnosis is unclear, endoscopic ultrasonography and fine-needle aspiration (**Option A**) can be performed for cytology, measurement of carcinoembryonic antigen level, and DNA analysis.

In the absence of high-risk features (e.g., main pancreatic duct dilation, cysts 3 cm or larger, change in the main duct diameter with distal parenchymal atrophy, and association with a solid mass), patients with mucinous cysts may undergo MRI surveillance (**Option B**), the frequency depending on many factors, including cyst size.

Surgical resection (**Option C**) of high-risk cysts is the only treatment option. In addition to the high-risk features just described, cysts in patients presenting with obstructive jaundice are also high risk. Surgical resection is recommended for nearly all mucinous neoplasms and main-duct intraductal papillary mucinous neoplasms if the patient is an appropriate surgical candidate. Mucinous cystic neoplasms occur almost exclusively in women in their fifth to seventh decades of life and are almost always located in the body or tail of the pancreas. These neoplasms have moderate malignant potential. Intraductal papillary mucinous neoplasms (IPMNs) are equally prevalent in men and women, usually appearing in their fifth to seventh decades of life. Branch-duct IPMNs are characterized by cystic structures that may appear throughout the pancreas. Imaging characteristics of main duct IPMNs include main pancreatic duct dilation and parenchymal atrophy. These neoplasms have variable malignant potential.

KEY POINTS

- Mucin-producing cysts, including intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, are thought to have malignant potential.
- Non-mucin-producing cysts, such as a serous cystadenoma, have no malignant potential.

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Item 70 Answer: D

Educational Objective: Diagnose *Helicobacter pylori* infection.

The most appropriate management for this young patient with uninvestigated dyspepsia is stool antigen testing for *Helicobacter pylori* (**Option D**). In the management of dyspepsia, benefits and costs favor a test-and-treat strategy for *H. pylori* infection. Patients who test positive for *H. pylori* should receive eradication therapy. Patients negative for

H. pylori on noninvasive testing are treated with empiric proton pump inhibitor (PPI) therapy. Appropriate noninvasive testing for *H. pylori* includes a monoclonal stool antigen test or a ^{13}C urea breath test.

If *H. pylori* test results are negative or *H. pylori* eradication fails to relieve the dyspepsia, an empiric trial of a daily PPI (**Option B**) should be followed for 4 weeks. Patients whose symptoms are not alleviated with PPI therapy should undergo further evaluation with upper endoscopy.

Serologic testing (**Option C**), which does not discriminate between past and active *H. pylori* infection, should be avoided. Particularly in low-prevalence populations, such as this patient, the test has a low accuracy for identifying active infection. A positive serologic test result may lead to unnecessary treatment in a substantial number of patients because of its high false-positive rates.

This patient is young and has no alarm features for malignancy, such as anemia, family history of gastrointestinal cancer, or melena; therefore, further invasive testing with upper endoscopy (**Option E**) is not indicated at this time. For the same reasons, CT (**Option A**) would be of low yield and would not warrant the cost or radiation exposure.

KEY POINTS

- For patients with dyspepsia, a "test and treat" strategy for *Helicobacter pylori* infection is recommended.
- In a person from an area with a low prevalence of *Helicobacter pylori*, a positive serologic result is likely a false positive and should be followed by a stool antigen test or a ^{13}C urea breath test.

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Item 71 Answer: D

Educational Objective: Diagnose Peutz-Jeghers syndrome.

This patient likely has Peutz-Jeghers syndrome (PJS) (**Option D**), which is caused by mutations in the *STK11* (*LKB1*) gene. PJS is a hamartomatous polyposis syndrome, and PJS-type polyps are found primarily in the small bowel as well as the stomach and colon. Small-bowel hamartomas develop at a young age (average age, 18.5 years), and patients may present with rectal bleeding (most commonly), bowel obstruction, and intussusception. A clinical diagnosis of PJS may be made when two of the following three criteria are met: two or more PJS-type hamartomatous polyps in the gastrointestinal tract; typical mucocutaneous hyperpigmentation (melanotic macules) in the mouth, buccal mucosa, nose, eyes, genitalia, or fingers; and family history of PJS. Patients with PJS have increased lifetime risk for multiple malignancies: colorectal (39%), gastric (29%), small bowel (13%), breast (32%-54%), ovarian/sex cord tumor with annular tubules (21%), cervical/adenoma malignum (1%), uterine (9%), testicular/Sertoli cell tumor (9%), lung (7%-17%), and pancreatic (11%-36%). The multiple melanotic macules present on this patient's lips are not seen in other familial polyposis syndromes. It is important to recognize that people without PJS may also have melanotic macules, most commonly on the lower lip, but macules may also be found on the gingiva, buccal mucosa, or tongue or within the genital mucosa. Solitary lesions are the rule, but multiple lesions suggest PJS.

Adenomatous polyposis syndromes (**Option A**) include familial adenomatous polyposis, which is caused by mutations in the *APC* gene, as well as *MUTYH*-associated polyposis, caused by bi-allelic loss of *MUTYH*. Mutations in polymerase proofreading genes *POLE* and *POLD1* are rare but are also associated with adenomatous polyposis. These latter syndromes have features of both Lynch syndrome and familial adenomatous polyposis. The dermatologic findings observed in this patient are not seen in adenomatous polyposis syndromes.

Mutations in the tumor suppressor *PTEN* gene cause *PTEN* hamartoma syndrome (also known as Cowden syndrome) (**Option B**) and are associated with a lifetime risk for colorectal cancer of 9% to 16%. Patients with this syndrome exhibit macrocephaly, facial trichilemmomas, lipomas, and oral papillomas as well as hamartomatous polyps.

Juvenile polyposis syndrome (**Option C**) is caused by mutations in *SMAD4* and *BMPR1A*. Patients often present with rectal bleeding in their teens or early twenties. Evaluation can reveal multiple juvenile polyps (>5 polyps) in the colon (98%), stomach (14%), and small bowel (14%). It is important to differentiate juvenile polyposis syndrome from sporadic juvenile polyps, which may be seen in 1% of children and are not considered syndromic.

KEY POINT

- The diagnosis of Peutz-Jeghers syndrome (PJS) is based on the presence of two of the following three criteria: two or more PJS-type hamartomatous polyps in the gastrointestinal tract; multiple melanotic macules in the mouth, buccal mucosa, nose, eyes, genitalia, or fingers; and family history of PJS.

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Item 72 Answer: D

Educational Objective: Manage fundic gland polyps.

The patient does not require follow-up upper endoscopy (**Option D**). Fundic gland polyps are the most common benign epithelial gastric polyp incidentally found on upper endoscopy. These polyps are typically asymptomatic, smaller than 1 cm, and located in the gastric fundus and/or gastric body; they can be solitary but are more often multiple. They can be sporadic or can result from long-term proton pump inhibitor (PPI) use (>12 months). Dysplasia is exceedingly rare; sporadic fundic gland polyps progressing to cancer have not been reported. In fact, dysplastic changes typically affect only polyps larger than 1 cm. Some polyp characteristics can raise concern: symptomatic polyps, polyps larger than 1 cm, polyps in the gastric antrum, or polyps with an abnormal appearance. In these patients, the polyp should be completely resected rather than being biopsied. Polyps later found to contain dysplasia on biopsy are also of concern, and repeat upper endoscopy should be promptly performed to completely remove these polyps. If fundic gland polyps are histologically confirmed and no dysplasia or concern for syndromic polyps is present (as in this patient), no further endoscopic follow-up is needed.

Universal recommendations for surveillance when dysplasia is found are lacking, although expert opinion suggests that initial surveillance upper endoscopy be pursued at 1 year (**Option A**), with the interval of subsequent upper endoscopies to be determined by findings, given the polyps' slow rate of growth, such as over 3 to 5 years (**Option B**). Repeat upper endoscopy should be considered at an even shorter interval, such as 6 months for polyps with high-grade dysplasia. Fundic gland polyps can be syndromic in association with the familial adenomatous polyposis syndrome. In this setting, dysplasia is common (present in 25% to more than 50% of polyps). The finding of a carpet of fundic gland polyps (>50 polyps) in a young patient, especially one not taking a PPI, and/or the presence of dysplasia should raise suspicion for familial adenomatous polyposis and prompt further evaluation with a colonoscopy. In the setting of PPI-induced sporadic fundic gland polyps with no strong indication for PPI use, discontinuation of PPI should be discussed, although the data are mixed on whether PPI-associated sporadic fundic gland polyps regress after PPI discontinuation.

Repeat endoscopy in 10 years (**Option C**) is not recommended for any gastric polyp setting.

KEY POINT

- Fundic gland polyps are the most common benign epithelial gastric polyp and require no endoscopic follow-up.

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H

Item 73 Answer: D

Educational Objective: Manage gastric ulcer surveillance.

The most appropriate next step in management is no further surveillance—no follow-up endoscopy is needed (**Option D**). Surveillance endoscopy is based on the concern that some gastric cancers present as gastric ulcers that initially appear endoscopically and histologically benign. However, this rationale is of limited clinical use and is not cost-effective. As such, no U.S. or Canadian gastroenterology society has recommended routine surveillance for gastric ulcers. Instead, the decision to perform surveillance endoscopy for a gastric ulcer should be individualized. Surveillance with endoscopy is not necessary in patients with a low risk for gastric cancer, such as this patient, who was taking an NSAID and had endoscopic findings suggesting a typical NSAID-associated gastric ulcer, unremarkable biopsy specimens from the ulcer, and symptom resolution with appropriate medical therapy.

Surveillance endoscopy may be considered in gastric ulcers that appear suspicious for malignancy, ulcers that were not biopsied at the time of index endoscopy, or ulcers with an unclear cause. Features of the ulcer that raise suspicion for malignancy include a dirty ulcer base, a raised ulcer border, and/or irregular ulcer margins. Ulcers larger than 3 cm should also be followed endoscopically given their increased risk for complications, including rebleeding, penetration, and/or perforation. Surveillance endoscopy may be considered in patients who remain symptomatic despite an appropriate course (8-12 weeks) of antisecretory therapy with a proton pump inhibitor (**Options A, B**).

Refractory ulcers (those failing to heal despite 8-12 weeks of antisecretory therapy) should be considered for surveillance endoscopy (**Option C**) until healing is documented or until the cause is defined, such as surreptitious NSAID use, high-gastrin states, or ischemia.

KEY POINTS

- Routine repeat upper endoscopy for gastric ulcer is not recommended.
- Repeat upper endoscopy for gastric ulcer is reasonable for ulcers that appear suspicious for malignancy, ulcers that were not biopsied originally, ulcers with an unclear cause, or continued symptoms despite adequate therapy.

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Item 74 Answer: A

H

Educational Objective: Treat acute cholecystitis with early surgery.

The most appropriate treatment is cholecystectomy before hospital discharge (**Option A**). This patient has acute cholecystitis. This condition is associated with severe right-upper-quadrant or epigastric pain lasting longer than 6 hours, accompanied by fever and tenderness in the right upper quadrant. A positive Murphy sign (inspiratory arrest during right-upper-quadrant palpation) may be seen on physical examination. Laboratory studies may show leukocytosis. Results of liver chemistries are not usually abnormal in acute cholecystitis unless choledocholithiasis is present. Acute cholecystitis can be diagnosed by ultrasonography showing gallbladder wall thickening and/or edema and a sonographic

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Murphy sign, elicited with compression of the right upper abdomen with the ultrasound probe. Treatment includes analgesia, intravenous antibiotics with gram-negative and anaerobic coverage, and cholecystectomy before hospital discharge.

Cholecystectomy during the initial hospitalization is associated with improved clinical outcomes and lower costs compared with delayed cholecystectomy (**Option B**).

Emergency surgery (**Option C**) is necessary for suspected gallbladder perforation or emphysematous cholecystitis (infection of gallbladder wall with gas-forming organisms, such as *Clostridium perfringens*). These conditions can be fatal if not treated urgently. The previous good health of the patient and her clinical stability argue against these rare diagnoses, and emergency cholecystectomy is not necessary in this patient.

Endoscopic retrograde cholangiopancreatography (ERCP) (**Option D**) would be indicated if choledocholithiasis (stones in the bile ducts) or cholangitis (infection of the bile ducts) were present. Common duct stones can be visualized on transabdominal ultrasonography, but in the absence of visualization, an elevated serum bilirubin level and dilated common duct on ultrasonography make the diagnosis likely. Cholangitis is suggested by fever, jaundice, and right-upper-quadrant abdominal pain. Cholangitis is potentially life-threatening; identified common bile duct stones should be removed urgently with ERCP, after which elective cholecystectomy should be performed during the initial hospitalization. This patient's laboratory and imaging findings do not suggest choledocholithiasis or cholangitis.

In patients who are not good candidates for cholecystectomy and do not respond to antibiotics, a percutaneous cholecystostomy tube or endoscopic drainage (**Option E**) can be considered. This patient is otherwise healthy and is a good candidate for surgery.

KEY POINTS

- Acute cholecystitis can be diagnosed by ultrasonography showing gallbladder wall thickening and/or edema and a positive Murphy sign elicited during ultrasonography.
- Treatment of acute cholecystitis includes analgesia, intravenous antibiotics with gram-negative and anaerobic coverage, and cholecystectomy before hospital discharge.

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Item 75 Answer: C

Educational Objective: Evaluate hepatic encephalopathy with a medication review.

The most appropriate next step in evaluation is medication review and reconciliation (**Option C**). Hepatic encephalopathy is a common manifestation of cirrhosis and results from insufficient liver function and portosystemic shunting. Manifestations include behavioral, cognitive, and motor abnormalities. Severity ranges from mild changes of psychomotor slowing to frank coma. Hepatic encephalopathy indicates decompensation of liver disease and signals worsening liver function. Immediate management centers on identifying precipitating factors and administering medications, such as lactulose, that decrease absorption of toxins, such as ammonia, from the colon. Common precipitants of hepatic encephalopathy include infections; gastrointestinal bleeding; exposure to toxins, such as alcohol; and medications with sedating properties, such as benzodiazepines and opiate analgesics. Use of these medications in patients presenting with hepatic encephalopathy must be discontinued. Identification of culprit drug exposures may involve a careful review of mediations with family members, including medications that were prescribed by other clinicians or that were not prescribed but are being used by the patient, such as opioids or benzodiazepines.

CT of the head (**Option A**) with or without contrast does not typically contribute diagnostic information. However, the risk for intracerebral hemorrhage is increased in this patient group, and the symptoms may be indistinguishable; therefore, brain imaging may be part of the diagnostic workup based on clinical suspicion. However, this patient has a history of anxiety and alcoholism, and a careful review of medications and exposure to other toxins, such as alcohol or opioids, is the appropriate next step in his evaluation.

Electroencephalography (**Option B**) to evaluate for subclinical seizure activity is also unlikely to yield diagnostic findings. It is typically reserved for evaluation of patients without evidence of common precipitants.

Minimal manifestations of hepatic encephalopathy can be detected on neuropsychiatric testing (**Option D**). "Minimal" defines the disease as having no clinical signs of encephalopathy, such as confusion or asterixis. Neuropsychiatric testing is of value because it can help predict the development of overt hepatic encephalopathy, indicate poor quality of life and reduced socioeconomic potential, and help counsel patients and caregivers about the disease. Neuropsychiatric testing will be of no value in this patient with overt encephalopathy.

KEY POINTS

- The first step in the evaluation of hepatic encephalopathy is the identification of precipitating factors.
- Common precipitants of hepatic encephalopathy include infections, gastrointestinal bleeding, alcohol, and medications with sedating properties, such as benzodiazepines and opioids.

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Item 76 Answer: D

Educational Objective: Perform endoscopic follow-up for intestinal metaplasia.

The most appropriate next step in management is surveillance endoscopy (**Option D**). Gastric intestinal metaplasia (GIM) is a premalignant condition; patients have up to a 10-fold increase in the risk for gastric cancer compared with the general population. The risk for GIM and progression to gastric cancer is largely mediated by a history of *Helicobacter pylori* infection, race and ethnicity, immigration status, age, family history, and other environmental factors, such as autoimmune metaplasia, infection with Epstein-Barr virus, high salt intake, consumption of pickled foods, and use of tobacco products. Although gastric cancer is the fifth most commonly diagnosed cancer worldwide and the third most deadly cancer worldwide (nearly 800,000 deaths annually), it is uncommon in North America, with an estimated incidence of only 6 in 100,000. Given the low risk for gastric cancer in the United States, routine use of endoscopic surveillance is not recommended for GIM. Surveillance should therefore be tailored to the characteristics of GIM in addition to family history, ethnicity, race, and immigration status. Risk factors for gastric cancer include the presence of incomplete or extensive GIM; having a first-degree relative with gastric cancer; being African American, Asian, and Hispanic; and/or being first- or second-generation immigrants from high-incidence areas, including South America, Central America, Mexico, Caribbean nations, East Asia, Southeast Asia, post-Soviet states, Iran, and Turkey. Individuals with higher risk should be considered for surveillance endoscopy based on shared decision-making in which the patient puts a high value on the possible increased risk for gastric cancer and a low value on the risks associated with repeat endoscopy. The optimal interval for surveillance endoscopy remains unknown; however, indirect data suggest a 3- to 5-year interval for endoscopy.

There is no evidence that long-term treatment with proton pump inhibitors promotes the development of GIM; therefore, omeprazole does not need to be discontinued (**Option A**).

Studies of antioxidant therapy with ascorbic acid (**Option B**) and β-carotene have not consistently demonstrated a benefit in patients with GIM; therefore, this treatment cannot be routinely recommended.

No randomized controlled trials have demonstrated that chemoprophylaxis with aspirin (**Option C**) or NSAIDs decreases the risk for gastric cancer or progression of GIM. Some evidence of benefit has been described in observational studies.

KEY POINT

- Gastric intestinal metaplasia is a premalignant condition; patients have up to a 10-fold increased risk for gastric cancer compared with the general population.

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Item 77 Answer: D

H

Educational Objective: Manage upper gastrointestinal bleeding in a patient taking anticoagulant therapy for atrial fibrillation.

The most appropriate management is reinitiating warfarin within 7 days (**Option D**). This patient had significant upper gastrointestinal hemorrhage related to peptic ulcer disease. He was appropriately initiated on an intravenous proton pump inhibitor, anticoagulation with warfarin was withheld, and endoscopic therapy was performed. In patients with significant bleeding and an INR less than 2.5, guidelines recommend not delaying endoscopy. Few prospective data are available to guide optimal timing of resuming anticoagulation after gastrointestinal bleeding. In general, if hemostasis is certain, anticoagulants should be restarted as soon as possible because the outcome of a thrombotic event is usually far worse than recurrent gastrointestinal bleeding. Retrospective data suggest that resuming anticoagulation (warfarin or direct oral anticoagulants) within the first week minimizes risk for 90-day thrombosis, without increasing risk for 90-day recurrent gastrointestinal bleeding.

In patients with atrial fibrillation for whom warfarin was discontinued, re-anticoagulation with low-molecular-weight heparin or unfractionated heparin (**Option A**) should be considered within 48 hours in patients at high thrombotic risk, such as those with a mechanical prosthetic heart valve in the mitral position, atrial fibrillation with prosthetic heart valve, or mitral stenosis. This patient has no indication for heparin bridging before reinitiation of warfarin therapy.

Resuming anticoagulation after 30 days would be associated with increased risk for thrombosis and death without a significant increase in risk for recurrent gastrointestinal bleeding. Therefore, permanently discontinuing warfarin (**Option B**) or delaying reinitiation of warfarin beyond 7 days (**Option C**) would not be appropriate.

KEY POINT

- In a patient with gastrointestinal bleeding, resuming anticoagulation within the first week after discontinuation minimizes risk for 90-day thrombosis, without increasing risk for 90-day recurrent gastrointestinal bleeding.

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Item 78 Answer: E

Educational Objective: Manage asymptomatic gallstones.

The most appropriate management is clinical observation (**Option E**). Gallstones are asymptomatic in most patients. Symptomatic gallstone disease manifests as colicky pain resulting from stimulation of the gallbladder in the presence of an obstructive cystic duct from gallstones or sludge. This pain is typically of relatively acute onset, is fairly severe and steady, and is located in the right upper quadrant or epigastrium. Pain may radiate to the right scapula and can be associated with nausea, vomiting, and diaphoresis, lasting 30 minutes to 6 hours. This symptom complex may be precipitated by eating a fatty meal, which causes gallbladder contraction. Patients with unrelenting right-upper-quadrant or epigastric pain, bothersome early satiety, or postprandial fullness generally do not have biliary colic. Asymptomatic gallstones are commonly discovered when patients undergo abdominal imaging (CT or ultrasonography) for unrelated reasons. Incidental gallstones do not typically cause symptoms, and prophylactic cholecystectomy is generally not recommended.

Cholecystectomy (**Option A**) is indicated in asymptomatic patients at high risk for gallbladder cancer, including patients with gallstones larger than 3 cm, porcelain (calcified) gallbladder, or gallbladder polyps larger than 1 cm in size. This patient does not have these risk factors.

Endoscopic retrograde cholangiopancreatography (ERCP) (**Option B**) would be indicated for choledocholithiasis (stones present in the bile ducts) or cholangitis (infection of the biliary tree). Choledocholithiasis can often be visualized on transabdominal ultrasonography or is suggested by an elevated serum bilirubin level and dilated common duct on ultrasonography. Acute cholangitis is characterized by fever, jaundice, and right-upper-quadrant pain. This patient's clinical findings do not suggest choledocholithiasis or cholangitis.

In patients who have indeterminate findings suggesting a common bile duct stone, magnetic resonance cholangiopancreatography (MRCP) (**Option C**) or endoscopic ultrasonography may be performed as a less invasive diagnostic alternative to ERCP. There is no role for MRCP or endoscopic ultrasonography, however, in the evaluation of a patient with asymptomatic gallstones without risk factors for gallbladder cancer or suspected choledocholithiasis.

Ursodeoxycholic acid (**Option D**) can be considered for dissolving cholesterol stones in patients with biliary colic who cannot tolerate surgery. This agent has no role in patients with low-risk, asymptomatic gallstones.

KEY POINT

- Incidental gallstones do not typically cause symptoms, and prophylactic cholecystectomy and other treatments are generally not recommended.

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Item 79 Answer: C

Educational Objective: Identify the proper screening strategy for Lynch syndrome.

The most appropriate screening strategy is upper endoscopy and colonoscopy (**Option C**). This patient has Lynch syndrome, which is caused by germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* or the epithelial cell adhesion molecule gene (*EPCAM*). Risks for colorectal cancer vary by gene mutation but range from approximately 50% to 80% lifetime risk. Individuals with Lynch syndrome are at increased risk for colorectal and endometrial cancers (most common), as well as other cancers, including tumors of the stomach and small bowel. The Amsterdam II criteria are specific but not sensitive for the diagnosis of Lynch syndrome. This patient's family fulfills the Amsterdam II criteria for Lynch syndrome, which states that a diagnosis is warranted if all of the following criteria are met:

- Three or more family members have a Lynch syndrome–associated cancer.
- Two or more successive generations are affected.
- One of the cancers was diagnosed before age 50 years.
- One affected family member is a first-degree relative of the other two affected family members.
- Familial adenomatous polyposis has been ruled out.
- Tumors have been verified pathologically.

Online prediction models, such as the PREdiction Model for gene Mutation5 (PREMM$_5$), can also help predict risk for Lynch syndrome or other hereditary gastrointestinal cancer syndromes.

Screening for colorectal cancer in patients with Lynch syndrome should begin between ages 20 and 25 years, or 2 to 5 years before the earliest cancer diagnosis in the family. The recommended screening modality is colonoscopy, which should be repeated every 1 to 2 years. Patients with Lynch syndrome are also at increased risk for stomach and small-bowel cancers. Upper endoscopy may be considered around age 30 to 35 years and should be repeated every 2 to 5 years. This patient should therefore undergo both upper endoscopy and colonoscopy, with careful inspection of the distal duodenum and terminal ileum. *Helicobacter pylori* testing should be performed at least once, and *H. pylori* should be eradicated if found.

Fecal DNA testing (**Option A**) and a fecal immunochemical test (**Option B**) are acceptable colorectal cancer screening strategies for average-risk patients but are not sufficiently sensitive for a high-risk patient who requires both colorectal and stomach/small-intestine cancer screening.

Routine wireless capsule endoscopy (**Option D**) is not recommended unless the patient has iron deficiency anemia in the absence of an obvious source of bleeding following upper endoscopy and colonoscopy.

KEY POINTS

- Lynch syndrome is caused by germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* or the epithelial cell adhesion molecule gene (*EPCAM*).
- Patients with Lynch syndrome should be screened for colon cancer with colonoscopy beginning at ages 20 to 25 years (or 2-5 years before the earliest cancer diagnosis in the family) and screened for stomach and small-bowel cancers with upper endoscopy beginning at age 30 to 35 years.

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Item 80 Answer: B

Educational Objective: **Evaluate dyspnea in a patient with cirrhosis.**

The most appropriate diagnostic test to perform next is echocardiography (**Option B**). Patients with cirrhosis and portal hypertension are at risk for hepatopulmonary syndrome and portopulmonary hypertension. In hepatopulmonary syndrome, the pulmonary vasculature becomes dilated, resulting in right-to-left shunting of blood and hypoxemia. Patients may present with characteristic findings of orthodeoxia (worsening oxygen saturation while upright) and platypnea (worsening sense of dyspnea when upright). Dyspnea on exertion suggests possible portopulmonary hypertension, wherein increases in pulmonary arterial pressure cause high right-sided heart pressures. This condition is less common than hepatopulmonary syndrome but carries a high mortality rate. Echocardiography is the best initial diagnostic test in a patient with suspected pulmonary hypertension. If the echocardiogram shows high right-side pressures, potential causes of pulmonary hypertension should be evaluated before portopulmonary hypertension is selected as the diagnosis.

In this patient with normal pulmonary examination and normal chest radiographs, CT of the chest (**Option A**) is not likely to be helpful. If pulmonary hypertension is confirmed, pulmonary function testing and high-resolution CT of the chest might be useful if interstitial lung disease is a consideration.

The diagnosis of hepatopulmonary syndrome should be suspected in patients with portal hypertension who have symptoms of dyspnea and evidence of hypoxia. Findings of intrapulmonary shunting with contrast administration, such as agitated saline during echocardiography (**Option C**), confirm the diagnosis. This patient's symptoms and findings are not compatible with hepatopulmonary syndrome, and echocardiography with agitated saline is not indicated.

Progressive exertional dyspnea is the most common symptom of chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH remains an underrecognized cause of pulmonary hypertension and requires a high index of suspicion. Ventilation-perfusion scanning (**Option D**) is the most sensitive indicator of CTEPH and should be performed in all patients for whom the diagnosis is suspected. However, the diagnosis of pulmonary hypertension should be confirmed first, and the initial diagnostic study for pulmonary hypertension is echocardiography.

KEY POINTS

- Features of hepatopulmonary syndrome include orthodeoxia (worsening oxygen saturation while upright) and platypnea (worsening sense of dyspnea when upright); echocardiography with contrast can confirm the diagnosis.

(Continued)

KEY POINTS *(continued)*

- Patients with cirrhosis and portal hypertension who present with dyspnea on exertion should be suspected of having portopulmonary hypertension; echocardiography is the initial screening test.

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Item 81 Answer: C

Educational Objective: **Manage nocturnal gastroesophageal reflux disease with lifestyle modifications.**

The most appropriate additional management in this patient with nocturnal gastroesophageal reflux disease (GERD) is to recommend lifestyle modifications (**Option C**). Weight loss and tobacco smoking cessation should be recommended to patients with GERD who are obese and smoke, respectively. Patients with nocturnal GERD should avoid late-evening meals by eating at least 3 hours before bedtime and should elevate the head of the bed. Avoidance of large meals and fatty foods that stay in the stomach for longer periods is also helpful if adherence can be maintained. Drastic changes in the diet are not generally recommended because they are difficult to maintain. However, if a trigger is identified, such as alcohol, it is reasonable to recommend elimination of that trigger from the diet.

Although some patients require dosage escalation to twice-daily proton pump inhibitor (PPI) therapy (**Option A**), directed lifestyle modifications should first be attempted for the patient's weekend symptoms, which are related to large late-night meals. Her symptoms are otherwise controlled with the existing drug regimen. Dosage escalation may be appropriate if a trial of lifestyle modifications is not successful.

Surgical treatments for GERD include laparoscopic fundoplication (**Option B**). However, surgery is infrequently required; indications include failure of optimal PPI therapy with documented evidence of ongoing acid reflux, desire to stop medication, and intolerable medication side effects. These indications do not apply to this patient.

Most patients with GERD have normal findings on upper endoscopy (**Option D**). Upper endoscopy is warranted in patients reporting dysphagia, weight loss, hematemesis, or failure to respond to treatment. Lifestyle modifications should be introduced before upper endoscopy.

Wireless esophageal pH testing (**Option E**) can quantify acid exposure in the esophagus, confirm adequacy of acid suppression therapy, and differentiate between acid and nonacid reflux. Because the patient has classic symptoms of GERD that are generally well controlled with a PPI and weekend symptoms that should be amenable to lifestyle modifications, wireless pH testing is unnecessary.

KEY POINTS

- Weight loss and tobacco smoking cessation should be recommended to patients with gastroesophageal reflux disease who are obese and smoke, respectively.
- Patients with nocturnal gastroesophageal reflux disease should avoid late-evening meals by eating at least 3 hours before bedtime and should elevate the head of the bed.

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Item 82 Answer: D

Educational Objective: Treat chronic pain in a patient with cirrhosis.

The most appropriate treatment is physical therapy (**Option D**). Patients with cirrhosis are at risk for metabolic bone disease and osteoporosis. Bone densitometry is thus indicated in patients with cirrhosis to screen for metabolic bone disease, and bone-fortifying therapy is indicated in patients found to have osteoporosis. The management of chronic pain can be challenging in patients with chronic liver disease because the recognized adverse effects of analgesic medications can be exaggerated in these patients. Nonpharmacologic approaches to managing chronic pain should always be considered because they will not exacerbate the manifestations of chronic liver disease. Therefore, physical therapy should be considered initially in this patient population. Other nonpharmacologic therapies, including local injection therapies and behavioral therapy, may also be beneficial.

The serotonin norepinephrine reuptake inhibitor duloxetine (**Option A**) is approved by the FDA to treat chronic low back pain and may be useful in select patients. However, duloxetine should be avoided in patients with hepatic dysfunction. Rare cases of hepatic failure (some leading to death) have been reported with use. Hepatitis with abdominal pain, hepatomegaly, and elevated aminotransferase levels with and without jaundice have all been observed.

NSAIDs, such as ibuprofen (**Option B**), inhibit the production of renal prostaglandins and can exacerbate renal dysfunction and worsen fluid retention in the setting of cirrhosis. Therefore, NSAIDs should be avoided in patients with cirrhosis, particularly those with renal impairment or ascites, such as this patient.

Opioid analgesics (**Option C**) can precipitate hepatic encephalopathy in patients with cirrhosis. Furthermore, these agents can cause vasodilation and hypotension in patients with more advanced liver dysfunction. Therefore, opioid analgesics should be avoided for pain management in patients with cirrhosis. If analgesics are required, low-dose acetaminophen, up to 2000 mg/d, is generally safe and well tolerated in patients with advanced liver dysfunction.

KEY POINTS

- Opioid analgesics can precipitate hepatic encephalopathy in patients with cirrhosis.
- Management of chronic pain in patients with chronic liver disease should always include physical therapy because it will not exacerbate the manifestations of chronic liver disease.

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Item 83 Answer: D

Educational Objective: Treat acute cholangitis.

The most appropriate treatment is urgent endoscopic retrograde cholangiopancreatography (ERCP) (**Option D**). This patient has acute cholangitis, an infection of the biliary tree that is heralded by the Charcot triad (fever, jaundice, and right-upper-quadrant pain). Cholangitis is potentially life-threatening; therapy should include immediate antimicrobial therapy targeting Enterobacteriaceae in combination with urgent decompression of the biliary tree with endoscopic sphincterotomy and stone extraction. Additionally, cholecystectomy should be performed during initial hospitalization or within 2 weeks to reduce the risk for subsequent complications.

Surgical drainage of the biliary tree, either open or laparoscopic (**Option A**), is reserved for patients with acute cholecystitis who cannot undergo ERCP or in whom ERCP has failed. The surgical objectives are biliary decompression with choledocholithiasis removal. ERCP biliary drainage is preferred over surgical drainage because of substantially lower morbidity and mortality.

Magnetic resonance cholangiopancreatography (**Option B**) is a valuable tool in evaluating the biliary and pancreatic ducts and may be indicated in the nonurgent evaluation of suspected choledocholithiasis. In this case, however, the patient has a life-threatening infection (acute cholangitis), and urgent decompression of the biliary tree is indicated. There is no need for further imaging before intervention because the stone has already been identified on ultrasonography.

Although cholecystectomy (**Option C**) is the treatment of choice for acute cholecystitis, it has an ancillary role in the management of acute cholangitis. In acute cholangitis, stone location is typically within the common bile duct rather than in the cystic duct (as in acute cholecystitis), and cholecystectomy does not result in decompression of the biliary tree. After the stones are removed with ERCP, elective cholecystectomy should be performed during the initial

CONT.

hospital stay to reduce the risk for additional complications from gallstones.

KEY POINTS

- Acute cholangitis is suggested by fever, jaundice, and right-upper-quadrant pain.
- The treatment of choice for acute cholangitis is antibiotics and biliary drainage with endoscopic retrograde cholangiopancreatography.

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Item 84 Answer: A

Educational Objective: **Treat a large gallbladder polyp.**

The most appropriate management is cholecystectomy (**Option A**). This patient has a gallbladder polyp. Incidental findings, including gallbladder polyps, are usually seen on 1% to 5% of gallbladder ultrasounds, as well as in resected gallbladders. Neoplastic adenomas are rare, representing less than 0.5% of polyps. The best predictor of a malignant or premalignant lesion is size; polyps greater than 1 cm are more likely to be neoplastic and should be treated with cholecystectomy if possible. Gallbladder polyps associated with gallbladder stones or primary sclerosing cholangitis are also more likely to be neoplastic. This patient has a polyp larger than 1 cm and therefore should be offered cholecystectomy.

If common bile duct dilation had been present on ultrasonography, two options could be considered: (1) endoscopic retrograde cholangiopancreatography (ERCP) (**Option B**) for patients with cholelithiasis and therefore a high likelihood of choledocholithiasis, and (2) magnetic resonance cholangiopancreatography for diagnostic evaluation if ultrasonography findings are indeterminate. Urgent ERCP is indicated for acute cholangitis, signaled by fever, right-upper-quadrant abdominal pain, and jaundice. This patient does not have a dilated common bile duct or ascending cholangitis, and ERCP would not be appropriate.

When cholecystitis is suspected and the ultrasound is not conclusive, hepatobiliary iminodiacetic acid scanning with ejection fraction (**Option C**) may help determine gallbladder function in symptomatic patients without evidence of larger stones. However, the issue in this case is not the function of the gallbladder but rather the risk for neoplasm of the gallbladder polyp.

Gallbladder polyps that are 5 mm or less may be monitored with repeat ultrasonography (**Option D**) in 12 months. If they have increased in size, cholecystectomy may be offered. Gallbladder polyps that are 6 to 9 mm may be monitored with ultrasonography in 6 months and then yearly thereafter. Cholecystectomy may also be offered if the polyp size has increased. Because this patient has a 1.5-cm polyp, follow-up ultrasonography would not be appropriate.

KEY POINTS

- Gallbladder polyp size greater than 1 cm is a risk factor for malignancy; treatment for such polyps should be cholecystectomy.
- Gallbladder polyps associated with gallbladder stones or primary sclerosing cholangitis are more likely to be neoplastic regardless of the polyp size.

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Item 85 Answer: D

Educational Objective: **Treat functional dyspepsia.**

The most appropriate next step in treatment is initiating a nortriptyline trial (**Option D**). This patient has functional dyspepsia, epigastric pain that lacks an identifiable cause. Symptoms that may accompany epigastric pain include fullness, nausea, vomiting, bloating, heartburn, or alteration in bowel habits; however, the epigastric pain must be the predominant symptom. A diagnosis of functional dyspepsia traditionally requires normal findings on upper endoscopy or an upper gastrointestinal series. In patients with functional dyspepsia for whom *Helicobacter pylori* infection is confirmed, eradication therapy should be pursued because it may relieve symptoms. Some evidence suggests that a subset of patients with functional dyspepsia are sensitive to acid; therefore, a proton pump inhibitor (PPI) should be the initial therapy. However, pooled studies indicate that about 70% of patients with functional dyspepsia still have dyspeptic symptoms after a 2- to 8-week PPI trial. Tricyclic antidepressants (TCAs) are effective in the treatment of functional dyspepsia. Pooled results of three clinical trials involving 339 patients with this disorder demonstrated superiority of TCAs over placebo (number needed to treat, 6). The adverse events of TCAs, such as constipation, dry mouth, urinary retention, and somnolence, can be minimized by initiating TCA therapy at a low dosage (e.g., 10 mg once daily) and slowly titrating the dose by 10-mg increments every several weeks.

Selective serotonin reuptake inhibitors, such as citalopram (**Option A**), have shown no superiority over placebo in the treatment of functional dyspepsia.

Studies directly comparing H_2 blockers vs PPIs for treating functional dyspepsia have found no difference in treatment efficacy. Switching from omeprazole to famotidine (**Option B**) is unlikely to improve this patient's symptoms.

Although prokinetic agents, such as metoclopramide (**Option C**), may also help a small subset of patients with functional dyspepsia, a TCA trial should be pursued first given the potential side effects of prokinetic agents, such as dystonia and tardive dyskinesia, and stronger evidence of efficacy for TCAs.

KEY POINT

- In patients with functional dyspepsia who do not respond to an initial trial of a proton pump inhibitor, therapy with a tricyclic antidepressant should be initiated.

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Item 86 Answer: B

Educational Objective: Manage mild, travel-related diarrhea.

The most appropriate treatment is loperamide (**Option B**). In the setting of recent travel, the most likely cause of acute diarrhea is infectious, with *Escherichia coli* being the most common agent. Viral (e.g., noroviruses) and protozoal (e.g., *Entamoeba histolytica*, *Giardia duodenalis*) pathogens are also possibilities. Traveler's diarrhea usually occurs within the first 2 weeks of travel and is usually self-limited, lasting about 4 days; however, life-threatening volume depletion or severe colitis with systemic manifestations can occur. Some travelers develop chronic diarrhea or a postinfective irritable bowel syndrome. Fluid replacement is the mainstay of treatment, preferably by the oral route, with solutions that contain water, salt, and sugar. Antimotility drugs such as loperamide and diphenoxylate can be used in patients with mild or moderate traveler's diarrhea and as adjuvant therapy in patients treated with antibiotics. Antimotility drugs should be avoided in patients with dysentery (severe diarrhea and bloody stools). Bismuth is another appropriate treatment for traveler's diarrhea because of its antimotility and antimicrobial effects.

Widespread use of antibiotics for traveler's diarrhea has been associated with the acquisition of multidrug-resistant bacteria. Therefore, antimicrobials are recommended only for moderate or severe disease. Treatment with azithromycin (preferred for travel to South Asia and Southeast Asia) or a fluoroquinolone (**Option A**) (with increasing concern for resistance and adverse reactions) is recommended for moderate to severe traveler's diarrhea. Rifaximin and rifamycin are minimally absorbed oral antibiotic alternatives. Neither rifaximin nor fluoroquinolone antibiotics are used in patients with dysentery.

Stool culture (**Option C**) is not indicated in patients with mild traveler's diarrhea because it is typically a self-limited illness. This patient with a 2-day illness can expect the diarrhea to improve in another 1 to 2 days. Microbiologic testing is recommended in returning travelers with severe or persistent symptoms or those for whom empiric therapy fails.

Stool molecular testing (**Option D**), aimed at a broad range of clinically relevant pathogens, is preferred when rapid results are clinically important or nonmolecular tests have not established a diagnosis.

KEY POINTS

- Antimotility drugs, such as loperamide, can be used in patients with mild or moderate traveler's nondysenteric diarrhea and as adjuvant therapy in patients treated with antibiotics.
- Antibiotics are not recommended for mild traveler's diarrhea.

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Item 87 Answer: A

Educational Objective: Treat *Helicobacter pylori* infection persisting after initial therapy.

The most appropriate next step in management is a 14-day course of bismuth, tetracycline, metronidazole, and omeprazole (**Option A**). This patient's fecal antigen test confirms persistent *Helicobacter pylori* infection despite a previous course of eradication therapy. The most common factors responsible for failure of eradication therapy are lack of adherence to the treatment regimen or resistance of the *H. pylori* strain to the antibiotics. Other factors that decrease efficacy of eradication therapy include smoking, diabetes, and genetic factors affecting metabolism of proton pump inhibitors. As a result, eradication rates are less than 80% for a treatment regimen consisting of clarithromycin, amoxicillin, and a proton pump inhibitor (**Option B**), largely due to clarithromycin resistance of some *H. pylori* strains. Antibiotic resistance also exists for metronidazole (**Option C**) and levofloxacin, although metronidazole resistance can be overcome with higher doses of metronidazole. Resistance to amoxicillin is rare. Given the importance of antibiotic resistance for treatment efficacy, salvage therapy should not include antibiotics that have been previously taken. Therefore, the combination of bismuth subcitrate or bismuth subsalicylate along with metronidazole, tetracycline, and a proton pump inhibitor is the preferred salvage regimen for *H. pylori* infection that has not responded to a previous eradication regimen containing clarithromycin. A 14-day course of therapy (rather than a 10-day course) should be used for persistent *H. pylori* infection. This four-drug regimen can be challenging given the pill count, length of therapy, and potential for adverse effects. It is therefore important to counsel patients about adhering to the regimen and the potential for adverse effects.

The fecal antigen test results are sufficiently accurate to confirm persistent infection, obviating the need for further testing (**Option D**). The test was done more than 4 weeks after completion of eradication therapy (to reduce false-negative results) and the result was positive; repeating the test 1 month later is unnecessary.

In this asymptomatic patient, repeat upper endoscopy (**Option E**) is unnecessary to obtain additional gastric biopsy specimens or to document interval healing of the duodenal ulcers.

KEY POINTS

- Salvage therapy for *Helicobacter pylori* infection should not include antibiotics that have been previously taken.
- The combination of bismuth subcitrate or bismuth subsalicylate along with metronidazole, tetracycline, and a proton pump inhibitor is the preferred salvage regimen for *Helicobacter pylori* infection.

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Item 88 Answer: B

Educational Objective: Manage high-risk upper gastrointestinal bleeding.

The most appropriate treatment is esomeprazole, a proton pump inhibitor (PPI), intravenously twice daily for 72 hours (**Option B**). Upper endoscopy should be performed within 24 hours in patients with acute upper gastrointestinal bleeding (UGIB). In this patient, endoscopy revealed a nonbleeding visible vessel within the ulcer base, which is classified as an ulcer with high risk for rebleeding. After endoscopy, patients with UGIB and ulcers with high risk for rebleeding (active bleeding, nonbleeding visible vessel, or adherent clot) should receive continuous-infusion PPI therapy for 72 hours or a PPI intravenously twice daily for 72 hours and remain in the hospital during that time. Intravenous PPI therapy is followed by an oral PPI twice daily for 2 weeks, followed by once daily for an additional 6 weeks. The risk for rebleeding in patients with high-risk ulcers that are successfully treated endoscopically is similar for patients who receive twice-daily intravenous PPI and those who receive continuous PPI infusion. Because of the higher costs associated with continuous infusion, twice-daily PPI is preferable given the similar clinical efficacy.

Initiation of broad-spectrum antibiotics for 7 days is recommended in all patients with cirrhosis and gastrointestinal bleeding even in the absence of ascites. This patient does not have cirrhosis; therefore, treatment with broad-spectrum antibiotics (**Option A**) is not indicated.

Octreotide (**Option C**) is an analogue of somatostatin that decreases splanchnic blood flow and lowers portal pressure; it should be initiated before endoscopic evaluation and continuously infused for 3 to 5 days after variceal hemorrhage. Octreotide is not routinely used in nonvariceal UGIB.

Patients with low-risk stigmata following recent UGIB (i.e., flat pigmented spot, clean-based ulcer) should receive once-daily oral PPI therapy, such as omeprazole (**Option D**), for 8 weeks. Following endoscopy, these patients can be fed within 24 hours and discharged from the hospital. This patient has a high-risk ulcer; after 72 hours of intravenous PPI treatment, he will require treatment with PPI orally twice daily for 2 weeks followed by once daily for an additional 6 weeks.

KEY POINTS

- Patients with ulcers at high risk for rebleeding (active bleeding, nonbleeding visible vessel, or adherent clot) should receive intravenous proton pump inhibitor (PPI) therapy for 72 hours, followed by an oral PPI twice daily for 8 weeks.
- Because of the higher costs associated with continuous infusion, twice-daily intravenous PPI therapy is preferable given the similar clinical efficacy for upper gastrointestinal bleeding.

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Item 89 Answer: C

Educational Objective: Treat *Candida* esophagitis.

The most appropriate treatment is oral fluconazole (**Option C**). This patient probably has *Candida* esophagitis given his dysphagia with odynophagia, HIV infection with low CD4 count, and oral thrush. In patients with these clinical characteristics, the provisional clinical diagnosis can be made and empiric treatment begun. The most common causative species is *Candida albicans*, which is treated with oral fluconazole.

Viral esophagitis, caused by herpes simplex virus (HSV) or cytomegalovirus, may also occur in immunocompromised patients. HSV esophagitis is treated with acyclovir, and cytomegalovirus is treated with ganciclovir (oral valganciclovir is also an option). Viral esophagitis, however, is typically associated more with odynophagia than with dysphagia. More important, the presence of oral thrush is highly predictive of *Candida* esophagitis; therefore, treatment with ganciclovir (**Option A**) or acyclovir is not indicated as initial therapy. Endoscopy with biopsy is needed to confirm the diagnosis of viral esophagitis and should be performed if the patient does not respond to empiric antifungal treatment.

Intravenous echinocandin therapy with caspofungin (**Option B**), micafungin, or anidulafungin may be used in hospitalized patients with *Candida* esophagitis refractory to azole therapy. This patient does not have an indication for intravenous echinocandin therapy.

Simultaneous infection with *Candida* and HSV necessitating dual therapy with fluconazole and acyclovir (**Option D**) would be unusual. The most likely diagnosis is *Candida* esophagitis, and empiric treatment with fluconazole alone is preferred. If viral esophagitis is suspected, endoscopy and biopsy are required for diagnosis and to direct therapy, rather than empiric antifungal and antiviral therapy.

If symptoms are atypical or do not respond to treatment, endoscopy with biopsy or cytologic brushings (**Option E**) may be performed to confirm the diagnosis and evaluate for other causes of dysphagia. However, the presence of oral thrush is highly predictive of *Candida* esophagitis in immunocompromised patients presenting with dysphagia and odynophagia. Infectious esophagitis can more rarely be caused by other viral, bacterial, and parasitic pathogens, including *Lactobacillus* species, β-hemolytic streptococci, *Cryptosporidium* species, *Pneumocystis jirovecii*, *Mycobacterium avium* complex, and *Mycobacterium tuberculosis*.

KEY POINTS

- *Candida* esophagitis can be diagnosed clinically in patients with dysphagia and odynophagia, immunosuppression, and findings of oral thrush.
- *Candida* esophagitis can be treated with oral fluconazole.

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Item 90 Answer: C

Educational Objective: **Evaluate suspected gastroparesis.**

The most appropriate next step in management is 4-hour gastric scintigraphy (**Option C**). This patient's presentation strongly suggests—but is not diagnostic of—diabetic gastroparesis. Her upper gastrointestinal symptoms and the retained food on upper endoscopy indicate delayed gastric emptying. However, definitive diagnosis of gastroparesis requires objectively demonstrating a delay in gastric emptying. American College of Gastroenterology guidelines state that the diagnosis of gastroparesis must be based on the combination of symptoms of gastroparesis, absence of gastric outlet obstruction or ulceration, and a delay in gastric emptying. Objective evidence of delayed gastric emptying is important because other conditions, such as accelerated gastric emptying, functional dyspepsia, *Helicobacter pylori* infection, and peptic ulcer disease, can present with similar symptoms. This patient reports many gastroparesis symptoms, which can include early satiety, postprandial fullness, nausea, vomiting, bloating, and/or upper abdominal pain. Her upper endoscopy excluded a mechanical obstruction of the stomach and *H. pylori* gastritis. To document a delay in gastric emptying, further testing must be performed. The three tests used are scintigraphy, wireless motility capsule, and breath testing using ^{13}C-labeled *Spirulina platensis*. Of these tests, scintigraphy of a solid-phase meal is considered the standard for diagnosis of gastroparesis because it quantifies the emptying of a physiologic caloric meal. The 4-hour solid-emptying study is preferred over shorter solid-emptying studies or sole liquid-emptying studies because those methods are less sensitive. The most reliable parameter to document a delayed gastric emptying is the percentage of retained gastric contents 4 hours after meal consumption.

Medical therapy for gastroparesis—erythromycin (**Option A**) or metoclopramide (**Option B**)—should not be initiated until the diagnosis is confirmed.

An upper gastrointestinal barium series (**Option D**) can exclude mechanical obstruction and other structural abnormalities of the upper gastrointestinal tract, but this confirmation has already been accomplished with upper endoscopy. A barium series cannot objectively assess gastric emptying.

Although poor glycemic control is known to further delay gastric emptying, there is no value in repeating upper endoscopy after better control of this patient's diabetes (**Option E**) to reassess for retained food.

KEY POINTS

- The diagnostic criteria for gastroparesis include a combination of compatible symptoms, absence of gastric outlet obstruction or ulceration, and an objectively measured delay in gastric emptying.
- Tests to document delayed gastric emptying include scintigraphy, wireless motility capsule, and breath testing; scintigraphy of a solid-phase meal is preferred.

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Item 91 Answer: B

Educational Objective: **Treat microscopic colitis.**

The most appropriate management is discontinuation of ibuprofen (**Option B**). The histologic finding of marked intraepithelial lymphocytosis in the context of a normal-appearing colon is compatible with lymphocytic colitis, a form of microscopic colitis. This form of inflammatory bowel disease comes in two predominant forms: lymphocytic colitis and collagenous colitis. The condition mostly affects middle-aged women and is characterized by abrupt or gradual onset of watery diarrhea that has a relapsing-remitting course over months to years, sometimes accompanied by weight loss and abdominal pain. Microscopic colitis can be idiopathic, but medications, including NSAIDs, proton pump inhibitors, and selective serotonin reuptake inhibitors, have been associated with its development. Management of microscopic colitis starts with discontinuation of potentially causative medications, in this case ibuprofen. This patient could be advised to substitute acetaminophen or, if that drug is not effective, a trial of topical NSAIDs; gastrointestinal toxicity is much lower with topical NSAIDs because of reduced systemic absorption.

Fecal calprotectin (**Option A**) can be of diagnostic utility in evaluating chronic diarrhea; an elevated level suggests colonic inflammation and warrants further investigation, such as colonoscopy. However, fecal calprotectin is not of diagnostic value in this case, for which colonoscopy has already established a diagnosis of microscopic colitis.

Oral budesonide (**Option C**), a glucocorticoid with extensive first-pass metabolism by the liver, is effective in the treatment of microscopic colitis. However, it is reserved for patients whose symptoms do not improve after other measures, such as cessation of associated medications (in this case ibuprofen) or symptomatic treatment with loperamide.

Oral prednisone (**Option D**) can be used as induction therapy in patients with other forms of inflammatory bowel disease (ulcerative colitis and Crohn disease), but these diagnoses are not supported by the patient's lack of endoscopically visible colonic abnormalities, such as ulcers, edema, or erythema. In addition, prednisone should not be used as first-line treatment of microscopic colitis because of its adverse effects.

KEY POINTS

- Microscopic colitis can be idiopathic, but medications, including NSAIDs, proton pump inhibitors, and selective serotonin reuptake inhibitors, have been associated with its development.
- Treatment of microscopic colitis starts with discontinuation of potentially causative medications, symptomatic treatment with loperamide, and possibly progression to oral budesonide.

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Item 92 Answer: D

Educational Objective: Manage dermatitis herpetiformis.

The most appropriate management is measurement of glucose-6-phosphate dehydrogenase activity (**Option D**). This patient with a history of celiac disease has a chronic pruritic vesicular rash on the elbows and knees. Dermatitis herpetiformis is a neutrophilic dermatosis caused by IgA antibodies against tissue and epidermal transglutaminase. It typically presents with intensely pruritic papules and fragile vesicles that rapidly break, leaving tiny erosions. A skin biopsy specimen will show numerous neutrophils stuffing the dermal papillae, and a granular pattern of IgA deposition will be seen on direct immunofluorescence. Most patients with dermatitis herpetiformis will have an underlying gluten-sensitive enteropathy. However, they are usually free of gastrointestinal symptoms; only 20% of patients with celiac disease will develop dermatitis herpetiformis. The distribution and morphology, in the context of a history of celiac disease, are compatible with dermatitis herpetiformis. This condition is treated with a gluten-free diet, but patients may have continued symptoms despite strict adherence to this diet. Such patients may respond to dapsone (**Option A**). Before initiation of dapsone therapy, it is necessary to check for glucose-6-phosphate dehydrogenase deficiency because individuals with this condition can develop hemolytic anemia when exposed to this medication. Methemoglobinemia, agranulocytosis, and a dapsone hypersensitivity reaction are additional adverse effects. If the patient exhibits normal glucose-6-phosphate dehydrogenase activity, dapsone can be initiated.

Topical glucocorticoids, such as hydrocortisone (**Option B**), can be helpful as an adjuvant treatment for pruritus in patients with dermatitis herpetiformis, but they are ineffective as monotherapy in inducing remission. When topical glucocorticoids are used, they should be administered along with dapsone and a gluten-free diet. Systemic glucocorticoids, such as prednisone, are usually ineffective in the treatment of dermatitis herpetiformis.

Hydroxychloroquine (**Option C**) is an immunomodulator that is widely used in systemic lupus erythematosus (SLE) and can be used as monotherapy to treat mild skin and joint symptoms. A rare variant of acute cutaneous lupus presents with vesicles and bullae; invariably, however, these patients have other systemic manifestations of SLE. Therefore, treatment with hydroxychloroquine is not indicated in this patient.

KEY POINTS

- Dermatitis herpetiformis typically presents with intensely pruritic papules and fragile vesicles that rapidly break, leaving tiny erosions, and is commonly associated with histologic and serologic evidence of celiac disease.
- Dermatitis herpetiformis responds rapidly to dapsone; testing for glucose-6-phosphate dehydrogenase deficiency is required before initiation of therapy.

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Item 93 Answer: D

Educational Objective: Treat chronic pancreatitis with tobacco avoidance.

The most appropriate additional treatment for pain is tobacco cessation (**Option D**). The patient has chronic pancreatitis. Long-term tobacco use is an independent risk factor for acute and chronic pancreatitis, as well as pancreatic cancer. It is synergistic with alcohol in promoting morbidity related to pancreatic disease. Initial therapy for chronic pancreatitis pain should entail lifestyle modification, including alcohol and tobacco cessation, and simple analgesics. No direct evidence addresses whether alcohol cessation alters the natural history of chronic pancreatitis pain. However, several case series have suggested that discontinuing alcohol use improves the pain in chronic pancreatitis but does not necessarily alter the progression to endocrine or exocrine dysfunction. There is no direct evidence that smoking cessation is beneficial in improving the natural history of chronic pancreatitis. However, case series have shown a decrease in the amount of pancreatic calcification progression when smoking cessation occurs at the time of diagnosis of chronic pancreatitis. Both alcohol and smoking cessation are strongly recommended in the American College of Gastroenterology (ACG) guideline on chronic pancreatitis. Amitriptyline and nortriptyline may reduce pain from neuropathic conditions and therefore may be useful in patients with chronic pancreatitis. ACG makes no recommendation for or against these drug therapies in patients with chronic pancreatitis.

Opioids, such as oxycodone (**Option A**), should be avoided in the long-term management of chronic pancreatitis. Although they may be helpful for analgesia in acute pancreatitis and during flares of chronic pancreatitis, they may lead to hyperesthesia and opioid tolerance. The ACG recommends that opiates may be considered to treat painful chronic pancreatitis only in patients for whom all other reasonable therapeutic options have been exhausted.

A large systematic review found conflicting evidence for the efficacy of pancreatic enzyme replacement (**Option B**) in pain control; however, enzyme therapy may improve fat absorption. The ACG makes a conditional recommendation not to use pancreatic enzyme supplements to improve pain in chronic pancreatitis.

Patients with chronic pancreatitis often experience pain in the setting of pancreatic duct obstruction due to duct stones and strictures. Although surgical approaches to pancreatic duct decompression (**Option C**) provide better long-term pain relief than endoscopic approaches, they are rarely first-line therapies; in addition, many surgeons operate only after endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful. This patient does not have evidence of pancreatic duct obstruction.

KEY POINT

- Alcohol and tobacco avoidance are strongly recommended for patients with chronic pancreatitis.

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Item 94 Answer: A

Educational Objective: Manage aspirin therapy after lower gastrointestinal bleeding.

The most appropriate management is to discontinue aspirin indefinitely (**Option A**). The U.S. Preventive Services Task Force recommends low-dose aspirin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) and colorectal cancer in adults aged 50 to 59 years with a 10-year ASCVD risk of 10% or higher who do not have an increased risk for bleeding. In those aged 60 to 69 years, the benefits of aspirin use for primary prevention are smaller and the decision to initiate low-dose aspirin in this population should be individualized. The American College of Cardiology and American Diabetes Association suggest that low-dose aspirin might be considered for ASCVD primary prevention in adults aged 40 to 70 years who are at higher ASCVD risk but not at increased bleeding risk. This patient recently experienced hemodynamically significant lower gastrointestinal bleeding from diverticulosis. Although this bleeding was successfully treated, he is at considerable risk for recurrent bleeding from his diverticulosis. Case series demonstrate early rebleeding, defined as before hospital discharge, in up to 16% of patients and late rebleeding, defined as 30 or more days after discharge (**Option B**), in up to 24% of patients. Reinitiation of an NSAID or aspirin further increases risk for rebleeding. This patient had been taking aspirin for primary prevention of ASCVD. Although he does have several cardiovascular risk factors (age, hypertension, diabetes, dyslipidemia), the risk for recurrent lower gastrointestinal bleeding is greater than the benefit of daily aspirin in preventing myocardial infarction or stroke. Therefore, he should not restart aspirin now (**Option C**).

Guidelines on the management of lower gastrointestinal bleeding recommend avoidance of aspirin for primary prevention of cardiovascular events in most patients, particularly those with bleeding due to diverticulosis or angiodysplasia. However, after an episode of gastrointestinal bleeding, aspirin for secondary prevention of ASCVD should not be routinely stopped. If aspirin is stopped, then it should be restarted as soon as hemostasis is achieved.

The addition of a proton pump inhibitor such as omeprazole (**Option D**) may provide some protection from upper gastrointestinal bleeding, but it will not protect this patient from recurrent lower gastrointestinal bleeding. In this patient aspirin should be discontinued.

KEY POINTS

- After an episode of gastrointestinal bleeding, aspirin for primary prevention of atherosclerotic cardiovascular disease should be discontinued.
- After an episode of gastrointestinal bleeding, aspirin for secondary prevention of atherosclerotic cardiovascular disease should not be routinely stopped; if aspirin is stopped, then it should be restarted as soon as hemostasis is achieved.

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Item 95 Answer: C

Educational Objective: Evaluate for possible celiac disease.

The most appropriate diagnostic test to perform next is repeating the tissue transglutaminase IgA test after resumption of a gluten-containing diet (**Option C**). The patient is mostly asymptomatic and has normal physical examination and laboratory findings. However, her celiac disease status is uncertain because she has been maintaining a gluten-free diet for the past year without having been tested for celiac disease. Her clinical improvement after starting a gluten-free diet may be due to celiac disease or to nonceliac gluten sensitivity, a clinical syndrome of unknown pathophysiology. Because gluten-containing foods can also contain nonabsorbable carbohydrates, such as fructans, they can cause gastrointestinal symptoms due to osmotic mechanisms, as well as fermentation by colonic bacteria. By definition, celiac disease must first be excluded before nonceliac gluten sensitivity is diagnosed. Although the tissue transglutaminase IgA level is normal, the patient's gluten-free diet reduces the sensitivity of this serologic test. Celiac disease testing should therefore be repeated while the patient is on a gluten-containing diet; gluten should be reintroduced daily, preferably for 1 to 3 months before testing.

Although *Clostridioides difficile* colitis can cause chronic diarrhea, the response of the patient's symptoms to a gluten-free diet make this diagnosis less likely. Therefore, testing for this pathogen (**Option A**) is not indicated.

Most patients with celiac disease carry *HLA-DQ2* or *HLA-DQ8* genetic susceptibility; however, these genes can be found in up to 40% of the general population. Therefore, genetic testing (**Option B**) can rule out disease but not confirm it. Genetic markers for celiac disease are stable throughout life, regardless of one's diet, and repeating testing for them is not useful. A positive result on a serologic test for celiac disease requires upper endoscopy with biopsies (**Option D**) from the duodenum to confirm the disease. If biopsy results suggesting celiac disease are obtained before serologic testing, confirmatory serologic testing should be performed. Findings on upper endoscopy and biopsy may be normal in a patient with celiac disease who has adhered to a gluten-free diet for the past year. Therefore, the most appropriate management is resumption of a gluten-containing diet and follow-up serologic testing.

KEY POINTS

- Serologic testing for celiac disease must occur while the patient is on a gluten-containing diet.
- Genetic testing for celiac disease with *HLA-DQ2* or *HLA-DQ8* can rule out celiac disease but not confirm it.

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Item 96 Answer: C

Educational Objective: Treat gallstone pancreatitis with early cholecystectomy.

The most appropriate management is laparoscopic cholecystectomy before hospital discharge (**Option C**). A multicenter, randomized, controlled trial showed that for patients with mild gallstone pancreatitis, same-admission cholecystectomy reduced rates of gallstone-related complications compared with cholecystectomy 25 to 30 days after hospital discharge (**Option D**). The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute-onset abdominal pain characteristic of pancreatitis (severe, persistent for hours to days, and epigastric in location, often radiating to the back), (2) serum lipase or amylase levels elevated at least three times the upper limit of normal, and (3) characteristic imaging findings. Because acute pancreatitis is most commonly caused by biliary disorders, patients with acute pancreatitis should undergo transabdominal ultrasonography. Transabdominal ultrasonography is preferred over CT for detection of gallstones because it has a higher sensitivity for detection of gallstones, avoids the risks associated with intravenous contrast, and is more cost-effective. Imaging during this patient's hospitalization revealed multiple small gallstones in the gallbladder. Her common bile duct is normal in size and without choledocholithiasis; therefore, it is likely that a stone has passed through the common bile duct. Gallstone-induced acute pancreatitis can be caused by obstruction of the pancreatic duct or the ampulla, causing bile to reflux back into the pancreatic duct.

Endoscopic retrograde cholangiopancreatography (ERCP) (**Option A**) may be considered in the setting of ascending cholangitis with choledocholithiasis or if ongoing biliary obstruction is confirmed. The presence of cholangitis is manifested by fever, jaundice, and right-upper-quadrant abdominal pain and, in severely ill patients, hypotension and altered mental status. Cholangitis is potentially life-threatening, and antibiotic therapy targeting gram-negative Enterobacteriaceae should be administered. Identified common bile duct stones should be removed urgently with ERCP, after which elective cholecystectomy should be performed during the initial hospitalization or within 2 weeks to reduce the risk for complications. This patient does not have cholangitis, choledocholithiasis, or biliary obstruction.

Endoscopic ultrasonography (**Option B**) and magnetic resonance cholangiopancreatography (**Option E**) may be considered if ongoing biliary obstruction is suspected. This patient requires neither examination because she is clinically improving, her laboratory values are normal, and the bile duct on ultrasonography is of normal caliber. These findings suggest that biliary obstruction is unlikely.

KEY POINTS

- Acute pancreatitis is most commonly caused by biliary disorders, and patients should undergo transabdominal ultrasonography for the detection of gallstones.
- For patients with mild gallstone pancreatitis, same-admission cholecystectomy can reduce rates of gallstone-related complications compared with cholecystectomy 25 to 30 days after hospital discharge.

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